CT-PET weighted image fusion for separately scanned whole body rat

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Purpose: The limited resolution and lack of spatial information in positron emission tomography (PET) images require the complementary anatomic information from the computed tomography (CT) and/or magnetic resonance imaging (MRI). Therefore, multimodality image fusion techniques such as PET/CT are critical in mapping the functional images to structural images and thus facilitate the interpretation of PET studies. In our experimental situation, the CT and PET images are acquired in separate scanners at different times and the inherent differences in the imaging protocols produce significant nonrigid changes between the two acquisitions in addition to dissimilar image characteristics. The registration conditions are also poor because CT images have artifacts due to the limitation of current scanning settings, while PET images are very blurry (in transmission-PET) and have vague anatomical structure boundaries (in emission-PET).

Methods: The authors present a new method for whole body small animal multimodal registration. In particular, the authors register whole body rat CT image and PET images using a weighted demons algorithm. The authors use both the transmission-PET and the emission-PET images in the registration process emphasizing particular regions of the moving transmission-PET image using the emission-PET image. After a rigid transformation and a histogram matching between the CT and the transmission-PET images, the authors deformably register the transmission-PET image to the CT image with weights based on the intensity-normalized emission-PET image. For the deformable registration process, the authors develop a weighted demons registration method that can give preferences to particular regions of the input image using a weight image.

Results: The authors validate the results with nine rat image sets using the M-Hausdorff distance (M-HD) similarity measure with different outlier-suppression parameters (OSP). In comparison with standard methods such as the regular demons and the normalized mutual information (NMI)-based nonrigid free-form deformation (FFD) registration, the proposed weighted demons registration method shows average M-HD errors: 3.99 ± 1.37 (OSP = 10), 5.04 ± 1.59 (OSP = 20) and 5.92 ± 1.61 (OSP = ∞) with statistical significance ($p < 0.0003$) respectively, while NMI-based nonrigid FFD has average M-HD errors: 5.74 ± 1.73 (OSP = 10), 7.40 ± 7.84 (OSP = 20) and 9.83 ± 4.13 (OSP = ∞), and the regular demons has average M-HD errors: 6.79 ± 0.83 (OSP = 10), 9.19 ± 2.39 (OSP = 20) and 11.63 ± 3.99 (OSP = ∞), respectively. In addition to M-HD comparisons, the visual comparisons on the faint-edged region between the CT and the aligned PET images also show the encouraging improvements over the other methods.

Conclusions: In the whole body multimodal registration between CT and PET images, the utilization of both the transmission-PET and the emission-PET images in the registration process by emphasizing particular regions of the transmission-PET image using an emission-PET image is effective. This method holds promise for other image fusion applications where multiple (more than two) input images should be registered into a single informative image. © 2012 American Association of Physicists in Medicine. [DOI: 10.1118/1.3672167]

Key words: PET, CT, deformable registration, image fusion, whole body registration

I. INTRODUCTION

In preclinical (small animal) diabetic research, positron emission tomography (PET) plays an important role in both the diagnosis of diseases and the evaluation of interventions. PET provides detailed three-dimensional information about the underlying physiology and functional processes of the diseased and interventions. However, PET lacks of anatomical details which makes relating function and anatomy difficult. Often, the PET scan is aligned to an anatomical image acquired via magnetic resonance imaging (MRI) or computed tomography (CT) to place functional information in an anatomical context. While there has been much work in aligning PET and anatomical images for the brain in human subjects,^{1–3} such methods are not suitable for small animal whole body registration. These methods have essentially assumed that the mapping between PET and MRI/CT is rigid. In the case of abdominal and whole body imaging, this assumption is no longer valid as even small changes in posture can result in nonrigid deformations in the abdomen. Even in combined PET/CT scanners when the CT and PET images are acquired serially (such as lung imaging), additional corrections for nonrigid deformations are needed.⁴ Furthermore, most PET and CT registration studies have used human images. Registration of whole body images of small animals requires specialized methods primarily because the scale of possible displacements and deformations is large resulting in poor convergence of standard methods.

In the case of whole body registration between PET and CT images, rigid and elastic registration methods^{5–7} have been proposed. Previous intermodal registration methods between PET and CT/MRI were mostly based on the maximization of mutual information (MI).^{8,9} Skalski *et al.*¹⁰ investigated whether different PET images are more suitable for CT/PET registration. This study compared two registration schemes: an direct fusion scheme based on an emission-PET and an indirect fusion scheme based on a transmission-PET. Here an emission-PET detects the γ -rays from the radiotracer absorbed in the body and a transmission-PET measures a photon source that is rotated around the object. The transmission-PET is used for attenuation correction and provides images with (often suboptimal) anatomical information. The direct fusion scheme registered the emission-PET directly to the CT. The indirect fusion scheme registered the transmission-PET to the CT and indirectly registers the emission-PET with the resulting transmission-PET/CT transformation. It was reported that the indirect scheme has smaller error than that of the direct scheme.¹⁰

Many studies have proposed registration algorithms designed for whole body images of small animals. Based on hierarchical registration, Baiker *et al.*¹¹ adopted an iterative closest point (ICP) rigid registration to align mice skeletons from CT images. Later, this method was extended and used to approximate organs around the skeletons using a local shape context and a thin-plate-spline.¹² Chaudhari *et al.*¹³ and Joshi *et al.*¹⁴ also registered small animal images and estimated internal organs based on manually identified land-

marks on a 3D mouse atlas using a 3D harmonic volume mapping¹³ or an elastic volume warping from the landmarks,¹⁴ respectively. Xiao *et al.*¹⁵ proposed a modified three-dimensional shape context matching method for aligning rat skeletons from CT images. This method combined the positional relationship of neighboring points with curvature information for correspondences of points to avoid any joint definition on the skeleton. Suh *et al.*¹⁶ proposed a method based on a combined surface registration using both bone and body surfaces for small animal whole body registration. Baiker *et al.*¹⁷ registered the skeleton, the lungs and the skin of an articulated animal atlas, yielding point correspondence of those structures in the first step. This correspondence is then used to regularize an intensity-based B-spline registration in the next step.

In this paper, we propose an automatic, three-dimensional, fully deformable whole body registration method between PET and CT images acquired using different scanners. For this purpose, we take advantage of both the transmission-PET and the emission-PET images in the registration process. Here, the transmission-PET scanning is routinely obtained during regular PET scanning procedure of rat for the purpose of attenuation correction, and then, it is not used anymore because the transmission-PET does not provide any functional/physiological information which is the main purpose of the PET scanning. However, we employ the already existing transmission-PET images again for the registering process in addition to the emission-PET image. The emission-PET image emphasizes important parts of the moving transmission-PET image by amplifying the intensity variation of the low-contrast transmission-PET image. For the registration algorithm, we developed a weighted demons registration method that can give preferences to particular regions of the transmission-PET image using an emission-PET image. Unlike MI-based registration algorithms that depend on the statistical information of voxel intensities, partial differential equation (PDE)-based registration algorithms such as demons registration¹⁸ can easily combine the weighting factor with the gradient of the voxel intensities. This feature results in the enhanced registration performance for low-contrast images like the transmission-PET images.

The innovation in this paper is the combined use of both the transmission-PET image and the emission-PET image within the same PET-CT registration process. As far as we know, this paper is the first attempted at combining both PET images in a single registration process. As Skalski *et al.*¹⁰ indicated, currently there are only two fusion schemes: indirect fusion scheme (use of transmission-PET image for emission-PET/CT fusion) and direct fusion scheme (use of emission-PET for emission-PET/CT fusion). This paper does not address the problem of motion correction related to the respiratory process. We validate our results using nine rat image sets using the M-Hausdorff distance similarity measure with two standard nonlinear methods: a symmetric demons algorithm¹⁸ and a free-form deformation (FFD) algorithm using a normalized mutual information (NMI) match metric.¹⁹

II. METHODS

Our image set for each rat consists of an emission-PET image, a transmission-PET image, and a CT image. An example image set is shown in Fig. 1. The data were derived from a CT/PET imaging study of pancreatic beta cell in rodent models of diabetes.²⁰ The PET and CT images were scanned on different machines resulting in different rat posture between each image pair. Dynamic PET images were acquired over 120 minutes for ^{11}C —*dihydrotetrabenazine* (DTBZ) ligands using the high resolution research tomography (HRRT). The final reconstructed images cover $90 \times 90 \times 207$ pixels with a pixel size of 1.2 mm for both transmission-PET and emission-PET. CT images were acquired using 512 projections, 50 kV/600 μA energy resulting in a resolution of $100 \times 100 \times 100 \mu\text{m}^3$. Since the micro-CT scanner was not big enough for the size of our rats, the rat was scanned in three parts, and then, the images were stitched together forming one CT image. The final CT images have $128 \times 128 \times 304$ voxels. This study was performed using Sprague-Dawley rats, average age 10 weeks. The rats were anesthetized using a RC2 Rodent Circuit manufactured by VetEquip with 2.5% isoflurane and placed in a temperature-regulated plexiglass cylinder equipped to maintain the rat under isoflurane anesthesia with access to the tail for catheter placement. The cylinder also had the additional advantage of preserving the posture of the rat mostly unchanged during the imaging session. PET imaging was performed first. Then, animals were moved (while still in the plexiglass cylinder and under anesthesia) to an adjacent facility containing the micro-CT scanner and imaged in approximately the same orientation. Euthanasia was performed post CT imaging.²⁰

II.A. Preprocessing

Each input (a high resolution CT reference image, a transmission-PET moving image, and an emission-PET weight image) first undergoes several key preprocessing step as shown in Fig. 2. In our particular experimental protocol,

FIG. 1. Registration between CT images and the pair of transmission and emission-PET images. There are a number of challenges here including (i) the multimodal nature of the registration, (ii) the relatively low resolution of the PET images, and (iii) the artifacts in the CT images due to their being acquired in three parts.

FIG. 2. Block diagram for weighted registration between CT and transmission-PET images using emission-PET weights. Key steps include: the creating of a weight image from the emission-PET, and histogram matching between the transmission-PET and CT image allowing inter-modality methods.

the rats were placed in cylindrical tubes prior to both the CT and PET imaging which appear as cylindrical rings in the images as shown in Fig. 3. The bed was eliminated using a semiautomated procedure implemented within BioImage Suite.²¹ To create the weight image in Fig. 2, the emission-PET image was intensity-normalized and smoothed to reduce the range of intensities. First, the emission-PET image was normalized via log-scale mapping of the intensities and scaled to a final intensity range of 0–100. The normalized emission PET was then smoothed with a median filter. For the rigid transform step in Fig. 2, we performed a three-dimensional affine registration using a NMI match metric.⁹ The emission-PET image was also transformed into CT space using the same rigid transform. We assumed that the emission-PET and transmission-PET images are already registered since these images are acquired during the same imaging session. Finally, the CT image and the rigidly-transformed transmission-PET image underwent a histogram matching process. The transmission-PET image has intensity characteristics that are very similar to the CT and, following histogram matching, an intramodal method can be used. We used 1024 histogram levels in the histogram matching.

II.B. Weighted demons registration

Thirion¹⁸ suggested an image-matching algorithm using a diffusion process based on the concept of Maxwell's demons in thermodynamics. The algorithm warps the shape of the object boundary depending on the position of the demons within the image domain. The demons' forces, which deform the object shape, are generated to reduce the

(a) Input CT image

(b) Input transmission-PET image

FIG. 3. Sagittal, coronal, and axial views for an input CT image and an input transmission-PET image. Both images have the cylindrical rings that are around the rats to keep them immobilized. Those rings are removed in the preprocessing step.

disparity between the source and the target images. Equation (1) describes the demons algorithm based on the optical flow equation.¹⁸ Here, $\mathbf{r}(\mathbf{X})$ is the reference CT image, $\mathbf{m}(\mathbf{X})$ is the moving transmission-PET image and $\mathbf{v}(\mathbf{X})$ is the displacement

$$\mathbf{v}(\mathbf{X}) = -\frac{(\mathbf{m}(\mathbf{X}) - \mathbf{r}(\mathbf{X}))\nabla\mathbf{r}(\mathbf{X})}{\|\nabla\mathbf{r}(\mathbf{X})\|^2 + (\mathbf{m}(\mathbf{X}) - \mathbf{r}(\mathbf{X}))^2}. \quad (1)$$

The transformation $\mathbf{T}$ is then updated by the local displacement field iteratively at each voxel $\mathbf{X}$ by $\mathbf{T}(\mathbf{X}) = \mathbf{X} + \mathbf{v}(\mathbf{X})$. In this paper, we used a symmetric version²² of the extended demons method to reduce local minima

$$\mathbf{v}(\mathbf{X}) = -\frac{2(\mathbf{m}(\mathbf{X}) - \mathbf{r}(\mathbf{X}))(\nabla\mathbf{r}(\mathbf{X}) + \nabla\mathbf{m}(\mathbf{X}))}{\|\nabla\mathbf{r}(\mathbf{X}) + \nabla\mathbf{m}(\mathbf{X})\|^2 + (\mathbf{m}(\mathbf{X}) - \mathbf{r}(\mathbf{X}))^2}. \quad (2)$$

The demons registration method is based on the intensity gradient of the input images making it suitable for intramodality registration. For intermodality registration, the demons registration method requires additional preprocessing stage. When the reference and the moving images are positively correlated, histogram matching is often sufficient preprocessing. However, as shown in Fig. 4, histogram matching does not sufficiently match the intensity variations of the transmission-PET image and the CT image. This difference in intensity

FIG. 4. Normalized intensity profiles of CT and transmission-PET images. (a) CT image, (b) the transmission-PET image of the same rat, and (c) normalized intensity profiles along the dotted line in (a) and (b). The normalization is separately done by each peak intensity value of CT and transmission-PET images on the line. The two peak points in CT graph in (c) corresponds to the vertebrae in (a).

variations makes conventional registration methods ineffective for our application. Hence, we propose a weighted demons registration method in which we amplify the intensity gradient of an image using a weight factor to capture minute variations of the intensity. We use the emission-PET image coregistered to the moving transmission-PET image as the weight factor. Equation (3) shows the displacement for the weighted demons registration in which the intensity gradient of the moving transmission-PET image is amplified by the weight factor $\mathbf{K}(\mathbf{X})$

$$\mathbf{v}(\mathbf{X}) = -\frac{2(\mathbf{m}(\mathbf{X}) - \mathbf{r}(\mathbf{X}))(\nabla\mathbf{r}(\mathbf{X}) + (\nabla\mathbf{m}(\mathbf{X}))\mathbf{K}(\mathbf{X}))}{\|\nabla\mathbf{r}(\mathbf{X}) + (\nabla\mathbf{m}(\mathbf{X}))\mathbf{K}(\mathbf{X})\|^2 + (\mathbf{m}(\mathbf{X}) - \mathbf{r}(\mathbf{X}))^2}, \quad (3)$$

$$K(x) = \begin{cases} 1 & \text{if } |m(x) - r(x)| < thr \\ W(x) & \text{others} \end{cases}, \quad (4)$$

where $W(x)$ is the intensity value of the corresponding voxels in the normalized/smoothed emission-PET image. This weight factor affects the displacement calculation of each voxel only when the intensity difference between the corresponding points in reference and moving image is larger than

a threshold [Eq. (4)]. The threshold prevents the weight factors over-fitting the registration when there is close alignment between the reference image and moving image. When $K(x) = 1$ for a voxel x , this method reduces to the original demons registration method. Our weighted demons registration method used three levels of resolution to search the displacement in the 3D data set: The finest image resolution was the original CT image size, which was $128 \times 128 \times 304$ voxels. The mid-image resolution was $64 \times 64 \times 152$ voxels, and the coarsest image resolution was $32 \times 32 \times 76$ voxels. Iteration numbers for each layer were set to 100, 100, and 50 iterations from the coarsest to the finest layer, respectively. The threshold value in Eq. (4) was set to 10. We used a Gaussian smoothing kernel with $\sigma = 2$ (voxel) to smooth the displacement field. The computational time for the whole registration process including three levels of resolution was around 36 min per each study using Intel core Quad 2.4 GHz processor with 8 GB memory. Note that the weighting method in this paper does not deal with the matching problem of images with different distributions of different modalities. Instead, it aims to ensure that the registration in more important areas is more accurate in the same way that weighted-least squares fits aims to preferentially fit the more important information. In the case of PET/CT, the important regions are those where we have high counts in the emission-PET; hence, we derived our weights from the emission-PET.

III. RESULTS

We present experimental results demonstrating the effectiveness of our proposed method. Following preprocessing and rigid registration (which was performed identically in all cases), we compared the registration result of the proposed method against two standard methods: the FFD-based method of Ruckert¹⁹ which uses a NMI metric suitable for multimodality registration, and the symmetric demons method¹⁸ which uses the same deformation model as our method. Both competing methods follow the indirect scheme of Skalski *et al.*¹⁰ described in Sec. I. We first describe qualitative results followed by a description of our accuracy validation experiments.

III.A. Comparison of registered images

An example result from the rigid registration part of the preprocessing is shown in Fig. 5. The cross-hairs indicate the same point on the liver boundary in all images. In the CT image [Fig. 5(a)], the liver boundary is clearly distinguishable from surrounding tissue. Likewise, in the emission-PET [Fig. 5(c)], the upper boundaries of the liver are also distinctive. However, in the transmission-PET image [Fig. 5(b)], dark regions around the upper boundaries of liver are difficult to distinguish. Although visual evaluation for whole body PET/CT registration is not easy, distinctive features such as upper borderlines of liver and bladder boundaries are not exactly aligned. This result shows the need of nonrigid registration.

The input images to each registration algorithm and their resulting images of the proposed algorithm and the compet-

(a) Reference CT image

(b) Rigid transformed transmission-PET images

(c) Rigid transformed emission-PET images

Fig. 5. Coronal, sagittal, and axial views for three-dimensional CT image (reference) and a rigidly-transformed PET images before deformable registration. The cross-hair in CT image indicates a point on the rat's liver boundary, and the cross-hairs in the transmission-PET and the emission-PET images indicate the corresponding points.

ing algorithms are shown in Fig. 6. The cross-hairs indicate the same point on the liver boundary in all images. The reference CT image, and rigidly registered transmission-PET (above) and emission-PET (below) images are shown in Figs. 6(a) and 6(b), respectively. The liver boundaries of the emission-PET image in Fig. 6(c) (left arrow) are well aligned to those of the CT image. Both the results of the unweighted demons method [Fig. 6(d)] and NMI-base FFD method [Fig. 6(e)] are not aligned as well as the proposed method. As aforementioned, both competing methods as well as our proposed method follow the indirect fusion scheme, which registers the transmission-PET image to the CT image and indirectly registers the emission-PET image with the resulting transmission-PET/CT transformation. Therefore, although we can see the high-contrast edges around the liver in the emission-PET images, those high-contrast edge information in the emission-PET images is not taken into the Thirion's demons registration process because the very smoothed transmission-PET image was solely used as an input image with the reference CT image, while the useful information around high-contrast edge in the emission-PET images is successfully implicated into the registration process in the proposed weighted demons method. In case of NMI-based FFD, the small deformation

FIG. 6. Coronal and axial views for (A) reference CT image, (B) rigid transformed PET images (top:transmission, bottom:emission). Panels C–E show the nonlinearly warped PET as registered using: (C) the proposed weighted method, (D) demons, and (E) NMI registration. The borderlines in the bottom of panels C–E indicate the liver contour for the result comparison purpose [The borderline of the reference CT image in (A) is the same with the borderlines of the emission-PET images in (C), (D), and (E)]. Left arrows in panels A and C indicate the correctly aligned liver borderline. Right arrows in panel A and C indicate the correctly aligned a small hollow around liver.

in the emission-PET image occur because the small variation of intensity in transmission-PET image do not contribute enough information in the histogram stage of the NMI calculation. Figure 7 shows registration results of another rat, where the emission-PET images are fused with the CT image after each registration method. The arrows in the images of the unweighted demons method and the NMI-based FFD methods indicate the registration error regions around bladder.

III.B. M-Hausdorff distance similarity measure

To quantitatively compare of our weighted demons method with other competing methods, we measured a maximum-likelihood Hausdorff distance (M-HD) (Ref. 23) between the CT image and the deformed emission-PET image. Since the transmission-PET does not provide functional information, we compare the CT and emission-PET images. The correct alignment of these two images is the goal of this work as they represent the best functional and anatomical information.

The Hausdorff distance (HD) is well known as an efficient similarity criterion for low-level object or image comparison in computer vision.²⁴ This similarity measure uses a set of points extracted by an edge operator. Since many medical images from clinical/preclinical settings tend to have faint boundaries and disconnected edges, Hausdorff distance is frequently used as a quantitative measurement of similarity.^{25–28} In this paper, we use a three-dimensional version of maximum-likelihood M-HD measure²³ using Canny edge-detector with a Gaussian smoothing kernel with $\sigma = 2.0$.

For two sets of edge positions in three-dimensional binary images with size I and J , $P = \{(p_1^x, p_1^y, p_1^z), \dots, (p_I^x, p_I^y, p_I^z)\}$ and $Q = \{(q_1^x, q_1^y, q_1^z), \dots, (q_J^x, q_J^y, q_J^z)\}$, the classical directed distance based on Euclidean norm, $h(P; Q)$, is denoted by

$$h(P; Q) = \max_{(p^x, p^y) \in P} D_Q(p^x, p^y), \quad (5)$$

$$= \max_{(p^x, p^y, p^z) \in P} \left\{ \min_{(q^x, q^y, q^z) \in Q} \|(p^x, p^y, p^z) - (q^x, q^y, q^z)\| \right\}, \quad (6)$$

where $D_Q(p^x, p^y, p^z)$ is defined as the minimum correspondent distance at point (p^x, p^y, p^z) to the set Q and $\|(p^x, p^y, p^z) - (q^x, q^y, q^z)\|$ represents the L_2 norm. However, this HD measure is sensitive to degradation caused by noise and occlusions.

To improve the M-HD measure for image matching, Sim *et al.*²³ proposed a M-HD measures based on robust statistics. The directed distance $h_M(P; Q)$ of the M-HD based on M-estimation is defined as

$$h_M(P; Q) = \frac{1}{I} \sum_{(p^x, p^y, p^z) \in P} \rho(D_Q(p^x, p^y, p^z)), \quad (7)$$

where $D_Q(p^x, p^y, p^z)$ is the minimum correspondent distance at point (p^x, p^y, p^z) to the set Q and the cost function $\rho(\cdot)$ has a threshold of distance to eliminate outliers as below.

$$\rho(x) = \begin{cases} |x|, & |x| \leq \text{OSP} \\ |\text{OSP}|, & \text{otherwise} \end{cases} \quad (8)$$

FIG. 7. A second registration example: The three panels show fused PET/CT images using (A) the proposed weighted demons registration method, (B) demons registration,¹⁸ and (C) NMI registration.¹⁹ The borderlines indicate the bladder contour for the result comparison purpose. Arrows indicate the error regions around bladder.

$\rho(\cdot)$ is convex and symmetric, and has a unique minimum value at zero. These properties make $\rho(\cdot)$ a reasonable cost function. The outlier-suppression parameter (OSP, unit: *voxel*) is a threshold to eliminate outliers. Outliers yielding large distance errors are discarded. When the OSP is not included (i.e., infinity), the M-HD is equivalent to the modified Hausdorff distance presented in Dubuisson *et al.*²⁹ Because the M-HD similarity measure is robust in the presence of outliers and occlusions, the M-HD measure can be used to compare the similarity of PET-CT images even though the edges are not fully generated from the PET images due to vague contours as shown in Fig. 8. In Fig. 8(a), there are many edges from the CT image due to high resolution of anatomical structures. However, there are comparatively simple edge lines in the edge image of the emission-PET [Fig. 8(b)] due to the radiotracer collecting only in specific tissues.

Table I shows the M-HD similarity measures of our weighted demons method with other competing methods. The “rigid transform” row in Table I shows the M-HD measure between the CT image and the emission-PET image after the rigid registration in the preprocessing stage. We use this measure as a baseline in comparing how each nonlinear method improved over the initial rigid alignment. In Table I, we performed a paired-T test ($p < 0.05$) comparing the M-HD metric between rigidly-transformed emission-PET image and the CT image to the M-HD metric between the nonrigidly registered emission-PET images and CT Image. Over the nine rat image sets, our proposed method outperforms the competing methods significantly reducing the M-HD measure for all three OSP voxel values. The unweighted demons algorithm failed to show any significant improvements over the initial rigid registration. The FFD

algorithm performed better than the initial rigid registration but only show significantly better results with a low OSP voxel value. The individual comparisons over the nine data-sets are shown in Fig. 9.

With larger OSP (10, 20 and ∞ voxels), the quantitative performance difference between our weighted demons and other methods becomes larger. This difference suggested that our proposed method shows stable performance independent of edge detection. As indicated in the earlier Section III B, we used the same fixed parameter (Canny edge-detector with a Gaussian smoothing kernel with $\sigma = 2.0$) for the edge detection throughout all of our experiments. We kept the edge detection related parameters fixed as edge detection is not a part of the proposed registration process but a part of the evaluation process. Basically, Hausdorff distance metric serves to check if a template edge image is present in a test edge image even in presence of noise or occlusion (when the target is partially hidden). A lower distance value indicates a better match. However, some noise edges (outliers) may lower the distance value (even smaller than the distance for true corresponding edges) in HD calculation producing a false higher similarity.³⁰ Thus, we used the M-HD which has the outlier-suppression function with various OSP values. The OSP is a cut-off parameter that excludes the effects of noise and nonlinearly corrupted data. This parameter is determined experimentally by the level of noise in each image pair; thus, a range of OSP values are used to show the robustness of the similarity. In our experiments, our proposed registration method shows the consistently low Hausdorff distance over the different OSP values. These constantly low HD values come from the true matching between corresponding edges rather than from the accidental outliers.

FIG. 8. Coronal, sagittal, and axial views for the edges of (a) CT image and (b) the deformed PET images by the proposed weighted demons registration method. The cross-hairs in edge of PET images indicate the corresponding point on the rat's liver boundary in reference CT.

TABLE I. Comparison of M-Hausdorff distance between edge-detected CT images and edge-detected emission-PET images with different OSP (unit: *voxels*). (N = 9 pairs of images, Unit: *voxels* [Average Hausdorff distance per edge voxel]).

Method	OSP = 10	T test	OSP = 20	T test	OSP = ∞	T test
Rigid transform	7.79 ± 1.04		9.05 ± 1.28		12.21 ± 2.17	
demons	6.79 ± 0.83	0.07	9.19 ± 2.39	0.84	11.63 ± 3.99	0.71
NMI-based FFD	5.74 ± 1.73	0.02	7.40 ± 7.84	0.08	9.83 ± 4.13	0.12
Proposed	3.99 ± 1.37	2.62×10^{-4}	5.04 ± 1.59	2.79×10^{-4}	5.92 ± 1.61	1.19×10^{-4}

IV. DISCUSSION AND CONCLUSIONS

We have presented a new three-dimensional whole body rat intermodal nonrigid registration method between CT and PET images using a weighted demons algorithm. We used both the transmission-PET and the emission-PET images in

the registration process by emphasizing particular regions of the transmission-PET image using an emission-PET image. We note that the evaluation of the results of nonrigid intermodal registration between PET and CT images are challenging because of the lack of easily available gold-

FIG. 9. Individual comparisons of M-Hausdorff distance between edge-detected CT images and edge-detected emission-PET images with different OSP over the 9 datasets. (Unit: Average Hausdorff distance per edge pixel).

standards. Hence, as a fallback, we used the M-HD metric to quantify registration performance. Experiments with nine rats demonstrate encouraging performance of our method over competitive techniques as evidenced by consistently lower M-HD metrics.

The novel insight in the proposed algorithm is the combination of the transmission-PET and the emission-PET images in a single registration process. Similar to Skalski *et al.*,¹⁰ we apply an indirect fusion scheme based on the transmission-PET and the CT images. This scheme is extended by using the emission-PET image as a weight image. Hence, regions where the intensity of the emission-PET is high are preferentially registered (treated as regions of high functional importance). This is effectively a weighted-least squares type fitting procedure between the two images where the emission PET image is used to generate the weights. Hence, a key step for our algorithm is the construction of the weight image from the emission-PET image. The original emission-PET image is normalized and smoothed to create the weight image whose values range from 0 to 100. As shown in Figs. 5 and 6, the brighter regions in the emission-PET are mainly distributed over the several abdominal structures like the liver, stomach, bladder and kidney. These form the high weight areas. However, the darker regions around those internal organs still have weights from about 10–60 and still contribute to the registration process. Only the very dark regions outside the skin have weights of zero and are excluded from the registration process. Therefore, since the weight image varies smoothly between the high and low weights, the weights smoothly influence the registration process.

As Mattes *et al.*⁴ indicated, evaluating the results of inter-modal registration between PET and CT images is challenging as a result of the lack of a gold standard. It is also almost impossible to create unbiased, consistent evaluation results from human assessment, even when relying on expert users. Therefore, as a fallback, we used the M-Hausdorff Distance as an evaluation criterion. The M-Hausdorff Distance is less affected by partially generated edges, and not affected by additional edges beyond the distance of OSP. (The Dubuisson *et al.*'s²⁹ Hausdorff distance ($OSP = \infty$) in Table I shows the pure distances between every pair of edges.) However, our method is still sensitive to errors in edge detection, which is an inherent limitation of the M-Hausdorff Distance measure. Moreover, the edge points themselves are not accurate enough because the PET images have poor spatial resolution and significant spill-over effect.

While the presented work focused on PET/CT registration in whole body small animal imaging, the proposed method can be generalized to other applications. Different PET tracers may have various performance levels using the direct and indirect fusion schemes of Skalski *et al.*¹⁰ For example, at the beginning of this project, we first tried the direct fusion schemes by directly registering the emission-PET and CT images. However, unlike Skalski *et al.*, we were not able to align the images of several rats. These differing results may be caused by PET tracers targeting organs that may not provide enough information for image to image registration. A tracer that only targets a single organ such as the pancreas

(unlike a FDG-PET which will target many organs) would not be suitable for the direct scheme. Furthermore the indirect scheme using such tracers may find a global match between the transmission-PET and CT images and not accurately align the important organs. Our method is more general to the type of PET tracer and imaging protocol. Additionally, in the case of combined PET/CT scanners, the proposed method would be applicable in cases such as lung imaging where the serially acquired CT and PET images need to be warped for proper alignment.⁴ Future work will include generalization to other multimodal imaging studies where images were acquired in separate scanners such as PET/MR, SPECT/MR, and SPECT/CT registrations.

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¹R. P. Woods, J. C. Mazziotta, and S. R. Cherry, "MRI-PET registration with automated algorithm," *J. Comput. Assist. Tomogr.* **17**(4), 536–546 (1993).

²J. J. Vaquero, M. Desco, J. Pascau, A. Santos, I. Lee, J. Seidel, and M. V. Green, "PET, CT and MR image registration of the rat brain and skull," *IEEE Trans. Nucl. Sci.* **48**, 1440–1445 (2001).

³N. Hayakawa, K. Uemura, K. Ishiwata, Y. Shimada, N. Ogia, T. Nagao-kae, H. Toyama, K. Oda, A. Tanaka, K. Endo, and M. Senda, "A PET-MRI registration technique for PET studies of the rat brain," *Nucl. Med. Biol.* **27**, 121–125 (2000).

⁴D. Mattes, D. R. Haynor, H. Vesselle, T. K. Lewellen, and W. Eubank, "PET-CT image registration in the chest using free-form deformation," *IEEE Trans. Med. Imaging* **22**, 120–128 (2003).

⁵M.-L. Jan, K.-S. Chuang, G.-W. Chen, Y.-C. Ni, S. Chen, C.-H. Chang, J. Wu, T.-W. Lee, and Y.-K. Fu, "A three-dimensional registration method for automated fusion of micro PET-CT-SPECT whole-body images," *IEEE Trans. Med. Imaging* **24**, 886–893 (2005).

⁶Y.-C. Tai, K. P. Lin, C. K. Hoh, S. C. H. Huang, and E. J. Hoffman, "Utilization of 3-D elastic transformation in the registration of chest x-ray CT and whole body PET," *IEEE Trans. Nucl. Sci.* **44**, 1606–1612 (1997).

⁷R. Shekhar, V. Walimbe, S. Raja, V. Zagrodsky, M. Kanvinde, G. Wu, and B. Bybel, "Automated 3-dimensional elastic registration of whole-body PET and CT from separate or combined scanners," *J. Nucl. Med.* **46**, 1488–1496 (2005).

⁸F. Maes, A. Collignon, D. Vandermeulen, G. Marchal, and P. Suetens, "Multimodality image registration by maximization of mutual information," *IEEE Trans. Med. Imaging* **16**, 187–198 (1997).

⁹C. Studholme, D. L. G. Hill, and D. J. Hawkes, "An overlap invariant entropy measure of 3D medical image alignment," *Pattern Recogn.* **32**, 71–86 (1999).

¹⁰J. Skalski, R. L. Wahl, and C. R. Meyer, "Comparison of mutual information-based warping accuracy for fusing body CT and PET by 2 methods: CT mapped onto PET emission scan versus CT mapped onto PET transmission scan," *J. Nucl. Med.* **43**, 1184–1187 (2002).

¹¹M. Baiker, J. Milles, A. M. Vossepoel, I. Que, E. L. Kaijzel, C. W. G. M. Lowik, J. H. C. Reiber, J. Dijkstra, and B. P. F. Lelieveldt, "Fully automated whole-body registration in mice using an articulated skeleton atlas," *ISBI 2007, 4th IEEE International Symposium on Biomedical Imaging*, Arlington, VA (IEEE, Piscataway, NJ, 2007), pp. 728–731.

¹²M. Baiker, J. Dijkstra, I. Que, C. W. G. M. Lowik, J. H. C. Reiber, and B. P. F. Lelieveldt, "Organ approximation in micro-CT data with low soft tissue contrast using an articulated whole-body atlas," *ISBI 2008, 5th IEEE International Symposium on Biomedical Imaging*, Paris, France (IEEE, Piscataway, NJ, 2008), pp. 1267–1270.

- ¹³J. Chaudhari, A. A. Joshi, F. Darvas, and R. M. Leahy, "A method for atlas-based volumetric registration with surface constraints for optical bioluminescence tomography in small animal imaging," *Proc. SPIE*, **6510**, 651024 (2007).
- ¹⁴A. Joshi, A. J. Chaudhar, C. Li, D. W. Shattuck, J. Dutta, R. M. Leahy, and A. W. Toga, "Posture matching and elastic registration of a mouse atlas to surface topography range data," *ISBI 2009, 6th IEEE International Symposium on Biomedical Imaging*, Boston, MA (IEEE, Piscataway, NJ, 2009), pp 366–369.
- ¹⁵D. Xiao, P. Bourgeat, J. Fripp, O. A. Tamayo, M. C. Gregoire, and O. Salvado, "Non-rigid registration of small animal skeletons from micro-CT using 3D shape context," *Proc. SPIE*, **7259**, 72591G (2009).
- ¹⁶J. W. Suh, D. Scheinost, D. P. Dione, L. W. Dobrucki, A. J. Sinusas, and X. Papademetris, "A non-rigid registration method for serial lower extremity hybrid SPECT/CT imaging," *Med. Image Anal.* **15**(1), 96–111 (2011).
- ¹⁷M. Baiker, M. Staring, C. W. G. M. Lowik, J. H. C. Reiber, and B. P. F. Lelieveldt, "Automated registration of whole-body follow-up microCT data of mice," *Lect. Notes. Comp. Sci.* **6892**, 516–523 (2011).
- ¹⁸J. P. Thirion, "Image matching as a diffusion process: An analogy with Maxwell's demons," *Med. Image Anal.* **2**(3), 243–260 (1998).
- ¹⁹D. Rueckert, L. I. Sonoda, C. Hayes, D. L. G. Hill, and D. J. Hawkes, "Non-rigid registration using free-form deformations: Application to breast MR images," *IEEE Trans. Med. Imaging* **18**, 712–721 (1999).
- ²⁰T. Singhal, Y.-S. Ding, D. Weinzimmer, M. D. Normandin, D. Labaree, J. Ropchan, N. Nabulsi, S.-F. Lin, M. B. Skaddan, W. C. Soeller, Y. Huang, R. E. Carson, J. L. Treadway, and G. W. Cline, "Pancreatic beta cell mass PET imaging and quantification with [¹¹C]DTBZ and [¹⁸F]FP-(+)-DTBZ in rodent models of diabetes," *Mol. Imaging Biol.* **13**(5), 973–984 (2010).
- ²¹X. Papademetris, M. Jackowski, N. Rajeevan, R.T. Constable, and L.H. Staib. BioImage Suite: An integrated medical image analysis suite, Section of Bioimaging Sciences, Dept. of Diagnostic Radiology, Yale School of Medicine. <http://www.bioimagesuite.org>.
- ²²J. P. Thirion, "Fast non-rigid matching of 3D medical images," Technical Report No. 2547, INRIA, Sophia Antipolis, France, 1995.
- ²³D.-G. Sim, O.-K. Kwon, and R.-H. Park, "Object matching algorithm using robust Hausdorff distance measures," *IEEE Trans. Image Process.* **8**(3), 425–429 (1999).
- ²⁴D. P. Huttenlocher, G. A. Klanderman, and W. J. Rucklidge, "Comparing images using the Hausdorff distance," *IEEE Trans. Pattern Anal. Mach. Intell.* **15**(9), 850–863 (1993).
- ²⁵Y.-T. Wu, C. Zhou, H.-P. Chan, C. Paramagul, L. M. Hadjiiski, C. P. Daly, Y. Zhang, B. Sahiner, J. Shi, and J. Wei, "Dynamic multiple thresholding breast boundary detection algorithm for mammograms," *Med. Phys.* **37**, 391–401 (2010).
- ²⁶J. Yan, B. Zhao, L. Wang, L. H. Schwartz, and A. Zelenetz, "Marker-controlled watershed for lymphoma segmentation in sequential CT images," *Med. Phys.* **33**, 2452–2460 (2006).
- ²⁷V. Chalana and Y. M. Kim, "A methodology for evaluation of boundary detection algorithms on medical images," *IEEE Trans. Med. Imaging* **16**, 642652 (1997).
- ²⁸C. Alberola-López, M. Martín-Fernández, and J. Ruiz-Alzola, "Comments on: A methodology for evaluation of boundary detection algorithms on medical images," *IEEE Trans. Med. Imaging* **23**(5), 658–660 (2004).
- ²⁹M.-P. Dubuisson and A. K. Jain, "A modified Hausdorff distance for object matching," *Proceedings of 12th IAPR International Conference on Computer Vision and Pattern Recognition*, Jerusalem, Israel (IEEE, Piscataway, NJ, 1994), pp. 566–568.
- ³⁰O. K. Kwon, D. Kim, and J. W. Suh, "Accurate M-Hausdorff distance similarity combining distance orientation transform map for matching visible-thermal face images," *Pattern Recogn. Lett.* **21**(7), 903–909 (2011).