Published in final edited form as:

IEEE Trans Nucl Sci. 2011 October ; 58(5): 2296–2302. doi:10.1109/TNS.2011.2163526.

Automatic Alignment of Myocardial Perfusion Images With Contrast-Enhanced Cardiac Computed Tomography

Tracy L. Faber [Member, IEEE],

Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA 30322 USA

Cesar A. Santana,

Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA 30322 USA

Marina Piccinelli,

Department of Mathematics and Computer Science, Emory University, Atlanta, GA 30322 USA

Jonathon A. Nye,

Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA 30322 USA

John R. Votaw,

Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA 30322 USA

Ernest V. Garcia, and

Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA 30322 USA

Eldad Haber

Emory University, Atlanta, GA 30322 USA. He is now with the Department of Mathematics, University of British Columbia, Vancouver, BC V6T 1Z2, Canada

Tracy L. Faber: tfaber@emory.edu; Marina Piccinelli: mpiccin@emory.edu; Eldad Haber: haber@math.ubc.ca

Abstract

Explicit fusion of perfusion data from Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) with coronary artery anatomy from Computed Tomographic Coronary Angiography (CTA) has been shown to improve the diagnostic yield for coronary artery disease (CAD) compared to either modality alone. However, most clinically available methods were developed for multimodal scanners or require interactive alignment prior to display and analysis. A new approach was developed to register the two distributions obtained either from a single multimodal imager or from separate scanners, and a preliminary validation was undertaken to compare the automatic alignment to interactive alignment by two experts.

Index Terms

Computer-aided diagnosis; image registration; nuclear medicine

I. Introduction

Fusing myocardial perfusion images (MPI) with computed tomographic coronary angiography (CTA) has been shown to improve accuracy for diagnosing coronary artery disease over reading either alone [1], [2] or by reading both in a side by side manner [3], [4]. Much of the early work focused on images obtained from dual PET/CT scanners, so that the two studies were already in close alignment and required little manual improvement for a good registration. Later work has addressed the problem of aligning scans obtained from separate scanners, in which the patient, and the heart, may be positioned differently. Clinically, cardiac scans from separate scanners are generally aligned interactively. A side from the time-consuming aspect of interactive alignment, judging the registration of two very different images that show very different features is quite difficult. An automatic method for fusing images from separate scanners would improve reproducibility and throughput, and perhaps even accuracy.

Fusion of thoracic images has primarily been addressed in the realm of eliminating differences from respiratory motion between the PET or SPECT and the CTA. In oncology, the PET image is mainly ^{18}F -fluorodeoxyglucose (FDG), which is taken up by almost every tissue in the body; thus, FDG images have an anatomic appearance to them—skin boundaries as well as thoracic and abdominal organs may frequently be visualized. This makes alignment of FDG and CT images much more tractable, and numerous non-linear techniques for performing this operation have been reported [5]–[7]. However, cardiac images are generally created using radiopharmaceuticals which are particularly myocardial-avid, and which are not well distributed to other tissues. In addition, in MPI images, alignment of other tissues, such as the lungs, does not imply that the cardiac regions are registered. Woo, *et al.* [8] showed, for example, that standard mutual information techniques applied to cardiac MPI and CTA images provides a suboptimal registration. In essence, alignment of MPI and CTA images requires some method of focusing in on the heart itself.

Baty, *et al.* [9] described model-based alignment of non-contrast CT with MRI, but presumed the PET was already in alignment with the CT, having been acquired from a hybrid scanner. Kurshid, *et al.* [10] described a method where left ventricles (LV) from both PET and CT images (without contrast) were segmented, and a surface registration was performed. This method was developed to account for respiratory motion between the PET and the CT, in order to improve attenuation correction accuracy. It also relies on the heart being nearly registered, as happens in hybrid machines. Woo, *et al.* [8] used automatic boundary detection of the LV from the MPI to create a piece-wise constant template that was then aligned to the CTA using optimization methods. This work is particularly elegant in that it aligns each frame of the gated MPI to the single frame CT, and determines which of those frames best fit the CTA. Then all of the MPI frames are warped to the matching frame and summed to create a static image with less motion blur, and which better matches the CTA frame. This method can be used with images obtained from separate scanners.

The main drawback of these last two methods is that they focus on the LV alone. The LV may be rotationally symmetric, and as it is detected from low resolution nuclear images, its boundaries tend to be quite smooth. The approach outlined in this manuscript includes the

RV from the MPI to attempt to reduce problems with rotational symmetry. In addition, it uses the MPI image itself rather than a segmented version, so that as much detail as possible can be included in the optimization function. When the LV and RV myocardium are aligned in both CTA and nuclear images, then the coronary arteries from the CTA are also aligned, so that clinically useful fusion displays of anatomy and perfusion may be created.

II. Methods

A. Alignment

The basic approach is illustrated in Fig. 1. In essence, this method attempts to make the CTA image look more like the MPI prior to automatic alignment using mutual information.

Transaxial CTA images were interpolated to a voxel size of $1 \times 1 \times 2$ mm, and an in-house volume-of-interest tracing software program was used to hand segment the epicardial and endocardial boundaries in each. Note that these boundaries were closed, so that the in and outflow tracts of the ventricles were capped. The natural results of this interactive tracing were binary images with 1s inside the myocardium and 0's everywhere else; i.e., a binary image consisting of the LV and RV myocardium ($c_M(x)$). This can be seen in Fig. 1-I. This segmented CTA image was inverted to create zeros in the myocardium and ones in the background and chambers, Fig. 1-II. The largest connected region (the background) was deleted, and the remaining objects (the chambers) were sequentially eroded until two objects remained; this was necessary because errors in tracing occasionally resulted in the LV and RV chambers remaining connected in some slices. The two eroded objects were then sequentially dilated with the dilatation constrained so that the new objects remained within those regions identified as chambers in the previous step. This was continued until all of the pixels in the original chamber object were relabeled as one of two objects. The left most region was chosen as the CTA LV ($c_{LV}(x)$). The total region of the CTA ventricles ($c_F(x)$), including both chambers and myocardium, was also created for later use, described below.

The CTA LV was then automatically reoriented into short axis slices using an adaptation of the method previously outlined by Faber *et al.* [11] This was simply because most of our MPI images are saved as short axis. If we were using transaxial images this step would not be necessary. Briefly, the best axis of symmetry in the mid transaxial slice was determined by comparing the slice after rotation with its mirror image. The best symmetry was found when the difference between the reoriented image and its mirror was minimized. Reslicing parallel to this axis created sagittal slices parallel to the LV long axis. The process was repeated, this time to find the best axis of symmetry in a mid sagittal slice. Again this axis was used for reslicing. The algorithm used for determining optimization was a global search over all reasonable LV orientation angles and centers. This is seen in Fig. 1-III.

The LV chamber was identified from the MPI using endocardial boundaries generated by our previously published methods for function quantitation [12], which are part of the Emory Cardiac Toolbox (ECTb). ECTb functional analysis on the short axis nuclear images provides an estimate of LV epicardial and endocardial boundaries. A binary image of the chamber, $m_{LV}(x)$ was then created by connecting the endocardial surface points on each slice and filling in the resulting connected region of interest, as shown in Fig. 1-IV.

The reoriented LV chamber from the CTA image was next aligned with the binary LV chamber created from the MPI by determining the best transformation $T_{LV}(x)$, over three dimensional translations and rotations, such that the sum of their product was maximized:

$$T_{LV}(x) = \arg \max_{T_{LV}} \sum_x m_{LV}(x) C_{LV}(T_{LV}(x)). \quad (1)$$

Here, the transformation, $T_{LV}(x)$, can be thought of as a mapping of every pixel in the CTA image of the LV chamber $C_{LV}(x)$ to the MPI of the LV chamber $m_{LV}(x)$. The direction set method of Powell [13] was used for optimization. This operation was performed mainly to get the images close to being in registration, so that alignment using myocardial information would be less likely to find an inaccurate local minimum. Example results of this step can be seen in Fig. 1-V.

The rigid transformation was then applied to the CTA myocardial mask $C_M(x)$ as well as the full binary CTA mask ($C_F(x)$) that included both LV and RV myocardium and chambers, as shown in Fig. 1-VI. The reoriented mask was dilated and smoothed with a Gaussian with a 2 cm FWHM:

$$\hat{C}'_F(x) = C_F(T_{LV}(x)) \otimes G_1(x). \quad (2)$$

Here, the $\hat{}$ symbol indicates a CTA image in the MPI space, and the “prime” (apostrophe) indicates a Gaussian smooth.

The original MPI image, $m^o(x)$ was multiplied by this mask, $\hat{C}'_F(x)$ to eliminate background and preclude improper matching of the CTA heart with bright extracardiac objects. This created an image containing mainly MPI myocardium:

$$m_M(x) = m^o(x) \times \hat{C}'_F(x), \quad (3)$$

where the $\times$ operator implies multiplication of one image by another in a pixel-by-pixel manner. The result can be seen in Fig. 1 -VI. Next, the masked MPI was transformed into the CTA space:

$$\tilde{m}_M(x) = m_M(T_{LV}^{-1}(x)), \quad (4)$$

where the $\sim$ symbol implies an MPI in the CTA space. The CTA binary myocardial mask $C_M(x)$ was Gaussian smoothed:

$$\hat{C}'_M(x) = C_M(x) \otimes G_2(x). \quad (5)$$

This Gaussian $G_2(x)$ had a FWHM of the MPI resolution, to create a binary image that was similar to resolution of the MPI, with reduced counts in thinner walls, including the RV.

Finally, mutual information between the masked MPI and smoothed binary CTA ventricular image was maximized to find the best rigid transform (translation and rotation) for the masked MPI:

$$T_M(x) = \arg \max_{T_M} I\{C'_M(x), \tilde{m}_M(T_M(x))\}. \quad (6)$$

Example results are shown in Fig. 1-VIII. This final transform $T_M(x)$ was used to reslice the original short axis MPI image into the space of the reoriented short axis space of the CTA image. Again, most of these steps are shown graphically in Fig. 1.

B. Evaluation

Twenty four patients from a previous study were chosen [3]. All of these patients had MPI and CTA within 3 months of each other. MPIs included both SPECT and PET and abnormal and normal studies. Sixteen of the patients were male and 7 were female; the average age was 57.9 ± 10.8 years. The breakdown of these studies is given in Table I.

All SPECT studies were either Tc-99 Sestamibi or Tetrofosmin, and all were performed at high dose stress using either a Siemens E-CAM or a GE Millennium MG camera. PET studies were all stress Rb-82 performed with 1480–2220 MBq using a GE Discovery ST PET/CT. Ten of the CTA studies were performed with an earlier generation 16 slice Siemens Sensation, the rest were performed either with a 64 slice GE LightSpeed or a 64-slice Siemens Sensation. The CTA protocol is discussed in detail in Santana [3], but briefly, a bolus of 100–120 cc of iodinated contrast was injected at the rate of 5 cc/second followed by a saline chase. Scan acquisition was initiated after a previously determined scan delay time using routine parameters (120 KVp, 600–800 effective mAs, pitch 0.2 with helical acquisition, 1690.75 mm² or 6490.6 mm² detector configuration, and 0.33–0.40 second gantry rotation time for the 16- and 64- slice CT scanners, respectively). Images were reconstructed using retrospective ECG gating at a phase of the R-R interval that allowed a relatively motion-free visualization of the three main coronary arteries. This phase ranged from 50% to 70% of R-R interval.

CTA boundaries from the interactive tracings were already available; short axis MPIs were traced in their original resolution to obtain their myocardial boundaries (both left and right). Again, both epicardial and endocardial surfaces were traced separately.

The binary images from both the hand traced MPI and CTA images were converted into a triangulated set of boundary points to permit accurate estimation of the distance between them. The final transform was used to transform the surface points generated from the binary MPI masks, and the distance between the CTA and MPI surfaces after automatic alignment was measured as part of the evaluation metric.

The gold standard for aligning MPI and CTA images is interactive expertise. To evaluate how automatic alignment compared with interactive, two experts interactively translated and rotated the short axis SPECT images to match short axis CTA images, where the short axis CTA images were obtained by using the parameters obtained from reorienting the masks as

described previously. This rigid transform was also used to transform the MPI surfaces, and again, distances between the interactively aligned MPI and CTA surfaces were computed for both of the experts' alignments. The difference the difference between x, y, and z translations and rotations obtained from automatic alignment and those obtained from the two interactive alignments were also measured.

In order to ensure that large perfusion defects did not adversely affect the automatic alignment, a separate analysis was performed on those patients with fixed defects (infarcts) greater than 10% of the myocardium, as quantified by the Emory Cardiac Toolbox. Regression analysis was performed between the size of the fixed defect in % of myocardium and for each of the 6 translational and rotational "errors" of the automatic technique. Because there were two gold standards, i.e., the two expert alignments, a "worst case" automatic alignment error was determined by taking the larger of the two interactive-to-automatic translational and angular absolute differences as the "error" in automatic alignment. For example, if experts 1 and 2 disagreed with the automatic alignment by 2 and 4 mm in the x direction, respectively, the value of 4 would be used as the x translation error for this patient. Then, for the same patient, if experts 1 and 2 chose rotations about the z axis that differed from the automatic alignment by 5 and -7° , 7° would be used as the ρ rotation error. This provided six separate regression analyses. For each, correlation coefficients were determined and their significance levels were tested.

III. Results

The algorithms were implemented on a standard PC, and required an average of 42 seconds to register the MPI to the CTA. Of course, this does not include the time required to hand-segment the CTAs. That operation required between 20 and 30 min, depending on the CTA and the user.

Distances between the MPI and CTA surfaces after alignment for the two experts and the automatic method are shown in Table II. These distances are not significantly different from each other. Direct comparisons between the angles and translations between the interactive and automatic methods are shown in Table III.

There was no significant difference between alignment accuracy for normal and abnormal studies; however, PET alignments were significantly more accurate than SPECT alignments for both expert and automatic alignments, as determined using a paired t-test on the distances between MPI and CT surfaces, at level $p < .01$. For the expert I alignment, average distance was 2.10 mm for PET vs. CTA but 2.57 mm for SPECT vs. CTA. For the automatic alignment, average distance was 2.02 mm for PET vs. CTA but 2.42 mm for SPECT vs. CTA.

Figs. 2–5 show two examples of alignment results from both interactive and automatic procedures. The first example, Figs. 2 and 3, shows an abnormal SPECT image; differences between SPECT and CTA surfaces were 2.66, 2.58, and 2.62 mm for the automatic and two interactive alignments, respectively. The second example, Figs. 4 and 5, shows a non-CAD study. In this patient, differences between PET and CTA surfaces were 1.89, 1.84, and 1.61 mm, respectively.

Table IV shows the worst case scenarios for the patients with medium-to-large infarcts. Correlation of defect size with alignment errors showed that rotations about the y axis (ϕ or left-to-right) and translations along the x axis were correlated with defect size ($p < .05$); however, differences were generally not large, and note that the correlation in the y rotation was *negative*. Larger differences were seen with rotations about the z axis (ρ , the LV long axis) but these did not significantly correlate with infarct size. In only one case did the two experts *both* choose a translation that was more than one-half of a pixel different than the automatic method. This was in fact in a patient with a fixed defect (patient #6 in Table IV: 5 mm from one expert and 4 mm from the other, both in the z direction). In only three cases did both experts choose an angle that was more than 5° different from the automatic method (which would lead to an error of about one-half pixel at the edge of the myocardium, depending on heart size). Only one of these rotations was in a patient with a fixed defect (patient #1 in Table IV: 16° from one expert and 12° from the other, both about the z axis).

An overlay display of patient #6 from Table IV is shown in Fig. 6. This figure demonstrates the difference in z rotation chosen by expert 2 compared to that chosen by both the automatic method and expert 1. The y translation (anterior-inferior) difference was larger between expert 1 and the automatic method. The z translation discrepancy is actually in both interactive alignments compared to the automatic.

IV. Discussion

Automatic alignment registers MPI images to CTA similarly to experts using an interactive program. Distances between the two surfaces are not significantly different between the automatic methods and interactive alignments; in fact, the difference between the two interactive alignments is similar to that between the automatic and interactive alignments. Note that because the MPI-to-CTA distance was measured using interactively traced MPI surfaces, and because this distance could be zero even if the alignment was imperfect (say, for a completely symmetric object), this measurement should be considered primarily as a comparison between interactive vs. automatic alignment methods rather than an absolute computation of registration error. Taken in this manner, the lack of significant differences between these distances implies that the automatic technique is similar in accuracy to interactive alignment. Visually, the similarity in distance maps in Figs. 2 and 4 can also be appreciated.

Differences between automatic and interactive alignments were not clearly related to size of fixed defects. Translation differences in the x direction did correlate positively with the infarct size; however, it would be expected that interactive alignment would also suffer when much of the myocardium is missing. Interactive alignments rarely both disagreed by more than $1/2$ pixel with the automatic alignment; although this was seen more frequently in patients with fixed defects (5% of motions in the fixed defect patients compared to 2% of motions in the reversible defect and normal patients).

An obvious limitation of this work is that it used interactively obtained CTA surfaces. This approach was chosen in order to separate the alignment accuracy from the segmentation accuracy. However, we and others have presented automatic methods for cardiac CTA

segmentation [14]–[16]. Commercial techniques are also available and have undergone clinical evaluation [17], [18]. Note that we are not implying that this method can be easily placed into the workflow of standard clinical systems; the output of a segmentation program must be compatible with the ventricle-only mask that this algorithm requires as a starting point. Nor would we expect that this approach will be used with interactive segmentation clinically. However, the existence of segmentation methods does imply feasibility, and we are currently developing automated segmentation methods which will provide the appropriate input to this fusion approach.

Note that the differences in rotations and translations for the two interactive alignments were significantly different in the x translation and about the z (long) axis. Significant differences in x-translation were also seen between the automatic and interactive alignments, as well. However, note that the translational differences were quite small, less than one pixel. The experts agreed more with each other about how to translate the MPI in the z-direction, along the long axis, than they did with the automatic program (although the difference was only significant for one of the experts). We hypothesize that this is due to the MPI being a static study and therefore smaller than the CTA, particularly in the long axis direction, so that there is no real perfect alignment between the two datasets. In no other case was the interobserver variability significantly less than the difference between the automatic and expert alignments.

This brings up the final limitation, that the method was validated using only the static, motion-blurred perfusion image, rather than on one frame of the gated image. This may be considered suboptimal, but in actuality most CTA/MPI alignments are performed on static perfusion images. In addition, the right ventricle is much less well visualized in the gated frames, so that the alignment accuracy about the LV long axis may be compromised by not using the summed study. The optimal approach would be to compensate for the cardiac motion in the gated MPI in order to match create a summed, “motion-frozen” frame to its corresponding CT frame. We are also developing these techniques. However, in order to keep the RV information we must develop a method that will warp the entire image, and not just the left ventricle, as has been done by Slomka, *et al.* [19].

While this method appears somewhat heuristic, it is actually quite straightforward. In essence, the CT is made to look like the nuclear image. The preprocessing does not use any tunable parameters and the alignment itself is quite standard. The use of a pre-registration step using binary images of the LV chambers, which can be defined in the MPI fairly well even when there is a perfusion defect, gets the two images in the ballpark. Masking out the extracardiac activity from the MPI means there is really nothing in the two images but the LV and RV myocardium to register. This preprocessing simplifies the final registration. As explained earlier, future work will focus on automatically segmenting the CTA, creating a motion-corrected summed MPI frame, and both preclinical and clinical evaluation.

V. Conclusion

This new automatic method of fusing CTA and myocardial perfusion images is comparable in accuracy to expert interactive alignment based on the limited study population used in this work. Additional preclinical and clinical investigations remain to be performed.

Acknowledgments

This work was supported in part by NIH Grant R01HL085417 and by EMTech Bio. T. L. Faber and E. V. Garcia receive royalties from the sale of the Emory Cardiac Toolbox and have equity positions in Syntermed, Inc., which markets both ECTb and the Emory Reconstruction Toolbox.

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Fig. 1.

From top to bottom are shown the following processing steps (I) Interactive tracing of myocardial boundaries in CTA. (II) Chamber identification and LV isolation from CT mask using location. (III) Automatic LV reorientation from CT LV mask using symmetry. (IV) Creation of LV chamber image from MPI based on midmyocardial points obtained from perfusion quantification. (V) Initial automatic alignment of CTA and MPI LV chambers, as described in (1). (VI) Reslicing of CT masks (myocardial and epicardial) using LV alignment parameters so as to match with MPI, as described in (2). (VII) Masking out extracardiac activity in MPI using extended CT epicardial mask, described in (3) (VIII) Final alignment of masked MPI to smoothed myocardial CTA, described in (6).

Fig. 2.

SPECT and CTA of a patient with an inferior defect. Top left shows CTA midmyocardial boundaries overlaid on short and horizontal long axis sections of the SPECT studies after alignment with the automatic method (top) and interactively by two experts (middle and bottom). Three dimensional views to the right of this figure show SPECT and CTA surfaces, with the SPECT surface color coded for its distance from the CTA surface, the scale is provided at the bottom of the figure; values are in mm.

Fig. 3.

Same patient as in Fig. 2; here the SPECT image is overlaid in color on the CTA image again for the automatic method (top), and the two experts (middle and bottom).

Fig. 4.

PET and CTA of a non-CAD patient. Top left shows CTA midmyocardial boundaries overlaid on short and horizontal long axis sections of the PET studies after alignment with the automatic method (top) and interactively by two experts (middle and bottom). Three dimensional views to the right of this figure show PET and CTA surfaces, with the PET surface color coded for its distance from the CTA surface. Color meanings can be seen on the color scale at the bottom of the figure; values are in mm.

Fig. 5. Same patient as Fig. 4. This image shows the PET image overlaid in color on the CTA image again for the automatic method (top), and the two experts (middle and bottom)

Fig. 6. SPECT overlaid on the CTA of a patient with triple vessel disease and a fixed anteroapical defect extending over 34% of the myocardium. From top to bottom are shown the automatic alignment, interactive alignment 1, and interactive alignment 2.

Table I
Patient Population

Diagnosis	SPECT	PET	TOTAL	%
Low likelihood	2	4	6	25%
Non CAD (stenosis < 50%)	2	2	4	17%
CAD (stenosis > 50%)	13	1	14	58%
TOTAL	17 (71%)	7 (29%)	24	100%

Table II
Distance Between CTA and MPI Surfaces After Alignment

	Interactive 1	Interactive 2	Automatic
Mean distance (nun)	2.32±1.82	2.15±1.66	2.21±1.73

Table III
Differences in Translations and Rotations Between the Two Interactive and the Automatic Alignments

Mean difference	X (mm)	Y (mm)	Z (mm)	$\theta^{(x)}$ (xz)	$\phi^{(y)}$ (yz)	$\rho^{(z)}$ (xy)
Interactive 1 to 2	-1.2±1.9*	.30±2.2	.56±2.1	-.53±3.2	-.63±3.2	4.2±5.9*
Interactive 1 to automatic	1.4±1.2*	.73±2.1	1.3±2.1*	-.66±3.1	1.2±4.0	1.1±4.5
Interactive 2 to automatic	2.6±1.1*	.42±1.3	1.0±1.9	-.76±2.0	.54±2.7	5.2±5.6*

* Difference is significantly different from 0 with $p < .01$.

Table IV
Rotational And Translational Absolute Differences Between The Interactive And Automatic Alignments For 6 Infarct Patients

Patient	infarct size (%)	X(mm) error	Y(mm) error	Z(mm) error	$\theta(^{\circ})$ error	$\phi(^{\circ})$ error	$\rho(^{\circ})$ error
1	20	3.1	.64	1.5	1.2	4.1	16.0
2	23	3.2	1.2	3.0	5.8	5.1	7.5
3	30	3.8	1.4	0.0	2.5	1.9	5.7
4	11	2.0	2.2	2.3	4.3	10.8	14.0
3	38	3.8	0.6	3.6	5.1	3.6	0.7
6	34	4.9	3.3	5.2	0.9	1.3	14.5
r		.87	-.46	.36	-.1	-.84	-.61
P		.02	.15	.48	.85	.04	.20