A rib-specific multimodal registration algorithm for fused unfolded rib visualization using PET/CT

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ABSTRACT
Respiratory motion affects the alignment of PET and CT volumes from PET/CT examinations in a non-rigid manner. This becomes particularly apparent if reviewing fine anatomical structures such as ribs when assessing bone metastases, which frequently occur in many advanced cancers. To make this routine diagnostic task more efficient, a fused unfolded rib visualization for $^{18}$F-NaF PET/CT is presented. It allows to review the whole rib cage in a single image. This advanced visualization is enabled by a novel rib-specific registration algorithm that rigidly optimizes the local alignment of each individual rib in both modalities based on a matched filter response function. More specifically, rib centerlines are automatically extracted from CT and subsequently individually aligned to the corresponding bone-specific PET rib uptake pattern. The proposed method has been validated on 20 PET/CT scans acquired at different clinical sites. It has been demonstrated that the presented rib-specific registration method significantly improves the rib alignment without having to run complex deformable registration algorithms. At the same time, it guarantees that rib lesions are not further deformed, which may otherwise affect quantitative measurements such as SUVs. Considering clinically relevant distance thresholds, the centerline portion with good alignment compared to the ground truth improved from 60.6% to 86.7% after registration while approximately 98% can be still considered as acceptably aligned.

Keywords: Molecular imaging, registration, 18F-NaF, bone, metastasis, visualization

1. INTRODUCTION
Bone metastases are common with certain cancer types, particularly in breast, lung, and prostate cancer [1]. These common tumor types accounted in 2013 for 42.0% and 42.5% of new cancer incidences in the U.S. in men and women, respectively [2]. Similar trends have been reported for other developed countries, e.g., the same tumor types accounted for 40.2% and 38.8% of new cancer incidences in Germany in 2010 [3]. Even though it is difficult to determine precisely how frequently different tumors metastasize to bone, it was observed that in many patients with advanced disease, the skeleton is a site of significant tumor burden. Overall, the most common sites of bone metastases are spine, pelvis, ribs, skull, and proximal femur [4]. Finding and reporting rib metastases in chest CT scans is often difficult and time consuming as it involves the manual reading of hundreds of axial CT slices and the visual tracking of changes across the axial slices for each rib. For this purpose different techniques for the automatic extraction of rib centerlines have been proposed (e.g., [5–7]) that enable an enhanced visualization of the unfolded rib cage [8], which is designed to make radiologists’ routine bone reading task more efficient and effective (see Fig. 1a-b).

Beyond that, $^{18}$F-NaF PET/CT has been proven effective for detecting bone metastases when considering information from both modalities. Here, $^{18}$F-NaF as radiopharmaceutical (in the following referred to as NaF) has the desirable characteristics of high uptake in osteoblastic lesions accompanied by rapid blood clearance resulting in very good signal-to-noise ratios. More specifically, in a study on 44 patients with high-risk prostate
cancer, sensitivities close to 100% were reported for detecting bone metastasis considering NaF-PET alone [9]. At the same time, it is well known that increased NaF uptake may also correspond to benign processes such as in fractures, cysts, or degenerative changes, potentially leading to high false-positive rates. As a consequence, it is highly desirable to correlate NaF lesions with CT using integrated PET/CT systems, which resulted in a specificity increase from 79% to 100% in the aforementioned study.

In multimodal PET/CT imaging a good alignment between the functional and anatomical data is of great importance. Even though being consecutively acquired, both modalities frequently show local misalignments due to breathing and patient movement. While small differences are often not significant when reviewing larger organs (hence rendering the scanner alignment as sufficient), they are in the case of fine structures such as ribs. Inaccuracies in the image alignment may complicate the visual correlation of PET and CT information in regions of interest or impede an unambiguous anatomical localization of regions with increased PET uptake. The latter is particularly important for precise reporting of present lesions as well as treatment response assessment, especially in patients with multiple metastases.

To this end, we propose a rib-specific multimodal registration algorithm, which optimally aligns NaF-PET and CT data along each individual rib. It takes advantage of the fact that ribs can be reliably detected and labeled in anatomical CT datasets using the automated centerline detection algorithms of Wu et al. [7]. The resulting rib centerlines serve as input to the registration algorithm along with the functional PET data. This work enables the fused visualization of unfolded ribs (Fig. 1c-d), which without registration would make misalignments caused by respiratory motion (cf. Fig. 3) more apparent. The proposed method is robust to variations in PET scanning protocol (e.g., reconstruction method or post-filter) as well as to inaccuracies in the automatically extracted CT centerlines, which are more prominent for clinical PET/CT data due to CT scans being typically acquired at lower resolutions and doses compared to fully diagnostic CT scans.

2. METHODS

Given rib centerlines extracted from CT [7] we seek to compute for each individual rib a rigid transformation matrix that optimally aligns the centerline with the corresponding PET image signal. The advantages of this method are twofold. First, while the overall respiratory motion can be only accurately modeled with deformable transformations, each individual rib can be assumed to move rigidly as an acceptable approximation, hence avoiding solving complex deformable registration algorithms such as [10]. At the same time, the registration algorithm focuses on the structures of interest avoiding other, more prominent image features to dominate the registration results. Second, a rigid rib-specific registration guarantees that PET rib lesions are not further deformed (relative to the CT) and can be easily integrated in the unfolded rib visualization algorithm described in [8]. Beyond that, the corresponding rigid transformation matrix of a selected rib can be easily applied to conventional axial views resulting in a good alignment between PET and CT of the structure of interest without applying any deformations, which otherwise may result in changes in tumor volumes or falsify corresponding standardized uptake values (SUVs).

The proposed method consists of the following steps: First, variations in the input SUVs caused by differences in reconstruction protocol and/or scanner recovery curves are compensated by applying a phantom-optimized filter to the clinical PET data [11], which allows the subsequent steps to be computed with static parameters. Then, a matched filter based registration algorithm as detailed in Section 2.1 is utilized to compute a rigid registration starting with the top-most rib of each side (“L1”, “R1”) of the rib-cage using the scanner alignment as initialization. The results are used as initialization to compute the registrations of the second ribs (“L2”, “R2”) and so forth until a rigid registration matrix is computed for every rib. While each rib is registered individually without considering neighboring ribs during optimization, this ordered registration scheme is designed to ensure that rib centerlines converge towards the correct rib in the PET volume and starts at the topmost ribs as these feature very distinct shapes and their movement is furthermore limited by the collarbone.

2.1 Matched Filter Based Registration Algorithm for Single Ribs

Using a bone-specific tracer such as NaF, the algorithm utilizes the advantageous property that some uptake can be observed even in healthy bone with almost no uptake outside the bone matrix. However, compared to tumor uptake, it is noteworthy that normal bone and consequently rib uptake is very weak and might be either
Figure 1. Visualization of the unfolded ribs using CT (a) based on automatically extracted rib centerlines (b). If the data has been acquired with a PET/CT scanner, an accurate alignment between the ribs in the anatomical and functional data allows the visualization and interpretation of fused unfolded ribs (c). At the same time, anatomical information such as rib labels can be propagated to the functional data to support characterization and reporting of lesions (d).

Figure 2. Fused unfolded rib visualization before (left) and after (right) rib-specific registration; using automatically extracted rib centerlines [7], a flattened view of each rib is displayed for efficient bone assessment [8] (top). The corresponding distances of each CT centerline point to the PET ground truth (GT) are visualized color-coded (bottom) with green corresponding to regions of good alignment, yellow to acceptable alignment, and red to unacceptable alignment.
Figure 3. Misalignment between CT and PET images taken during the same scan due to breathing-induced rib motion. Typically, the CT part is acquired at breath hold while the PET acquisition is an average over multiple breathing cycles and hence mostly corresponds to an exhale state.

completely missing in some regions of the rib or might be hidden due to spill-out and partial volume effects of regions with higher uptake, such as lesions or the vertebral column. This would make the direct detection of rib centerlines from PET very challenging. However, it allows to align existing centerlines efficiently between both modalities if starting not too far off from the optimal result. Given the known rib shape (which may locally include errors due to an imperfect CT centerline extraction result), we compute a rigid transformation $T$ applied to the CT centerline $A$ that minimizes an energy function $E$ evaluated along $A \circ T$ in the PET volume.

Assuming an ideal bone-specific radionuclide distribution inside the ribs and a non-ideal point spread function for the scanner [12], the expected rib profile $I$ orthogonal to the centerline can be modeled by a Gaussian kernel $h_\sigma$ with zero mean and variance $\sigma^2$. As a consequence, the centricity of any centerline point $p$ along an intensity profile $I$ sampled at orientation $v$ orthogonal to the rib-centerline can be estimated by computing the matched filter response between $I(p,v)$ and the target profile $h_\sigma$. Moreover, the alignment in 3D can be efficiently estimated by casting multiple rays $v_i$ with $i \in [1,N]$ at different angles orthogonal to the rib centerline and combining the matched filter responses. Finally, the resulting energy function $E(A)$ for rib $A$ equals the sum of filter responses at each centerline point $p \in A$ normalized by the maximum observed intensity $I_{\text{max}}(p) = \max_i I(p,v_i)$ along the rays computed for each point $p$ to compensate for local intensity differences along the centerline:

$$E(A) = \sum_{p \in A} \frac{1}{I_{\text{max}}(p)} \sum_{i=1}^{N} I(p,v_i) \ast h_\sigma$$

In practice, the first derivatives of signal and kernel are matched to compensate for constant additive signal components in combination with Powell’s conjugate direction method to determine the optimal transformation matrix $T^*$ for rib $A$ using a rigid transformation parameter space $\Gamma$ using ITK*.

$$T^* = \arg \max_{T \in \Gamma} E(A \circ T)$$

The parameters of this method, namely, length $L$ and variance $\sigma^2$ of the filter kernel $h_\sigma$, the number of rays per centerline point $N$, and the sampling distance of centerline points have been empirically optimized based on 4 training cases from the database of available cases that are further detailed in the following section.

*The Insight Segmentation and Registration Toolkit, www.itk.org
3. RESULTS

A total of 24 NaF PET/CT datasets, routinely acquired at multiple clinical sites on different Siemens scanner models (Biograph Sensation 16 and Biograph TruePoint + TrueV), have been randomly divided into 4 training and 20 test cases. The resolution of the CT volumes varied between 1.5 − 5.0 mm in slice thickness, whereas the PET resolution varied between 3.3 − 5.0 mm in slice thickness with voxel sizes between 4.0 − 5.4 mm (in-plane). Rib centerlines have been automatically extracted from all CT scans employing the method described in [7] and only major errors have been semi-automatically edited (i.e., missing centerlines have been added and centerlines that jump from one rib to neighboring ribs have been corrected) in two instances. Additionally, all rib centerlines in the corresponding PET scans have been manually delineated by identifying a number of control points along each rib to define a smooth Catmull-Rom spline representation. To prevent inaccuracies in the CT centerline to influence the validation of the registration algorithm, each CT centerline has been geometrically aligned to the corresponding manual PET centerline using the iterative closest point (ICP) algorithm [13] and the results have been subsequently visually reviewed. The thus transformed CT centerlines are considered to be optimally aligned to the PET volume and serve as ground truth (GT) for validating the presented registration algorithm. The parameters of the utilized energy function (1) have been optimized based on the training cases and the resulting algorithm has been applied to the remaining 20 unseen datasets consisting of 476 individual ribs with approximately 250 000 rib points.

The necessity and benefits of a rib-specific registration for fused unfolded rib visualization are exemplarily highlighted in Figure 2a-b. Without further registration, rib regions with increased PET uptake may be visualized on the wrong rib (A') instead of being superimposed to the corresponding CT region (A) or may appear more diffuse (B) due to sub-optimal alignment. In the worst case scenario, a PET-positive region may not be visualized at all in the unfolded view (C) if the region does not overlap with any rib due to respiratory motion. As a consequence, distances between centerline points and the corresponding ground truth are classified into three categories (‘good’, ‘acceptable’, ‘unacceptable’) depending on clinically relevant tolerance thresholds. In practice, a ‘good’ alignment will most likely result in a good correlation between PET-positive lesions and the corresponding anatomical information. The alignment is considered still ‘acceptable’ if PET-positive lesions can be most likely identified in the resulting unfolded view, whereas an unambiguous association to the corresponding anatomical location may not be given. Finally, the alignment is classified as ‘unacceptable’ if resulting displacements may cause a lesion to be completely missed or assigned to the wrong rib. Moreover, displacements orthogonal to the centerline (\(d_\perp\)) are given more weight than distances along the centerline (\(d_\parallel\)) due to the increased likelihood of a lesion to be visualized on a neighboring rib or even to be completely missed. The resulting distance measure equals the \(l^2\)-Norm of \(d_\perp\) and \(0.5 \times d_\parallel\) and is denoted in the following by the unit

![Figure 4](https://example.com/figure4.png)

Figure 4. Performance of the proposed algorithm evaluated on approximately 250 000 rib points. Left: Histogram of distances between CT centerline points and PET ground truth before (top) and after registration (bottom). The vertical dashed lines correspond to the thresholds of 4.5 mm and 9 mm used for classifying the results into three categories (the unit [mm] corresponds to a normalized distance measure as detailed in Section 3). Right: Table summarizing the proportions of centerline points in each of the three categories.

<table>
<thead>
<tr>
<th>Alignment</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>60.6%</td>
<td>87.7%</td>
</tr>
<tr>
<td>Acceptable</td>
<td>32.7%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Unacceptable</td>
<td>6.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Mean distance</td>
<td>4.6 mm</td>
<td>2.6 mm</td>
</tr>
</tbody>
</table>
Figure 5. Box plots of the performance of the registration algorithm grouped by rib index. On each box, the central mark denotes the median, the edges of the box the 25th and 75th percentile. The whiskers extend to the most extreme (considered) data points while outliers are plotted individually.

[nnm]. Using thresholds of 4.5 nmm and 9 nmm determine the colors in Figure 2c-d.

The quantitative evaluation results can be analyzed for each individual rib point or grouped by ribs or patients. When comparing the histogram profiles shown in Fig. 4 before (top) and after (bottom) registration, one can see that the centerline portion with good alignment has been significantly increased (from 60.6% to 86.7%) while 97.7% (from 93.3%) can be still considered as acceptably aligned. Averaging the distance measure for each centerline, the achieved improvements by the registration algorithm varied depending on the position of the ribs. Figure 5 shows the average distances of each rib to the ground truth as box plots. Here, the rib index corresponds to the position of the rib within the rib cage with rib index 1 corresponding to the top-most rib without differentiating between left and right ribs. That is, each box consists of 40 datapoints from 20 patients unless single ribs were not visible in the input volumes. One can notice that even though the misalignment is fairly homogenous before registration (Fig. 5a) that the residual alignment error is particularly low for middle ribs after registration (Fig. 5b). This may be explained by the fact that ribs for which the registration algorithm performed better were on average longer than those ribs with poorer registration performance.

When comparing the centerline distances on a patient-per-patient basis, Fig. 6a shows that the average alignment has been improved for almost all cases with only a small number of cases remaining mostly unchanged. The same can be observed when examining Fig. 6b showing the 95th percentile distance value for each patient before and after registration. This trend is further detailed in Figure 7, which provides additional statistical information on the average distances on a rib-by-rib basis grouped by patient, i.e., each box consists of 24 datapoints unless again single ribs were not visible in the input volumes. Fig. 7a shows the distance distribution before and Fig. 7b after applying the proposed method, whereas Fig. 7c shows the distribution of differences in the alignment accuracy achieved by the algorithm. In total 81.1% of all ribs showed an improved alignment after registration.

4. CONCLUSIONS

We have presented a multimodal registration algorithm that enables the fused unfolded rib visualization of CT and NaF PET images for the efficient assessment of rib lesions. The algorithm optimizes a matched filter response evaluated along each CT rib centerline resulting in a rib-specific rigid transformation matrix. Compared to conventional algorithms, this approach solely focuses on the clinically relevant target regions, i.e., ribs, to achieve high registration accuracies while preventing other more prominent image features to dominate the registration outcome. We have applied the algorithm to 20 PET/CT cases resulting in significant alignment improvements for the majority of cases. After registration, approximately 87% of all centerline points can be classified as well aligned and 98% as still acceptably aligned. These results provide confidence in the feasibility of fused unfolded rib visualization for the efficient assessment of rib metastasis using NaF PET. In the future we are planning to extend the algorithm to other rib-specific tracers such as $^{99m}$Tc-MDP SPECT.
Figure 6. Scatter plot of average distances per patient (left) and the 95th distance percentiles (right).

Figure 7. Detailed analysis of the registration performance grouped by patient. For every patient the average distance of each individual rib centerline to the ground truth is computed before (top left) and after (top right) registration and represented as box plots. The distribution of distance differences is shown at the bottom. Here, a negative distance difference corresponds to a reduced difference to the ground truth and hence to an improvement in the alignment.
REFERENCES


