Penalized PET/CT Reconstruction Algorithms with Automatic Realignment for Anatomical Priors

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Abstract—Two algorithms for solving misalignment issues in penalized PET/CT reconstruction using anatomical priors are proposed. Both approaches are based on a recently published joint motion estimation and image reconstruction method. The first approach deforms the anatomical image to align it with the functional one while the second approach deforms both images to align them with the measured data. Our current implementation alternates between image reconstruction and alignment estimation. To evaluate the potential of these approaches, we have chosen Parallel Level Sets (PLS) as a representative anatomical penalty, incorporating a spatially-variant penalty strength to achieve uniform local contrast. The performance was evaluated using simulated non-TOF data generated with an XCAT phantom in the thorax region. We used the attenuation image in the anatomical prior. The results demonstrated that both methods can estimate the misalignment and deform the anatomical image accordingly. However, the performance of the first approach depends highly on the workflow of the alternating process. The second approach shows a faster convergence rate to the correct alignment and is less sensitive to the workflow. Interestingly, the presence of anatomical information can improve the convergence rate of misalignment estimation for the second approach but slow it down for the first approach.

I. INTRODUCTION

Penalized maximum-likelihood (PML) image reconstruction using penalties derived from anatomical images, such as computed tomography (CT) or magnetic resonance (MR) images, has been shown to be effective in improving object delineation and reducing quantitative error in many studies [1]–[10]. However, in order to utilize the structural information without incurring artifacts, a good alignment between the anatomical and functional images is essential [6], [9], [11], [12]. This is challenging in practice because these images are most likely obtained separately or sequentially. Even with a multi-modality scanner that performs simultaneous acquisition (e.g., Siemens mMR system and GE Signa PET/MR), good alignment between the acquisitions is still difficult to achieve due to the different time scales of the scans. For the misalignment involving non-rigid deformation, for instance due to respiration, the assumption is even harder to satisfy and accurate image segmentation and co-registration (which are difficult and time consuming) are often required [13], [14].

In many cases, anatomical information can be derived from the attenuation image. Since the literature on solving the misalignment issue between a priori anatomical information and the functional information is quite limited, we instead seek ideas from a similar but previously studied problem in thoracic PET imaging, in which a potentially misaligned CT or MR-derived attenuation map is used for the attenuation correction. As for PML image reconstruction using anatomical priors, the misalignment induced by patient respiration degrades resolution of the reconstructed image and introduces artifacts where large movement or deformation of organs is observed [15], [16]. Although these methods are intended to be used for having a better attenuation corrected image from emission data, they offer insights into resolving the misalignment between the anatomical attenuation map and the functional emission image.

This study will concentrate on imaging of the thorax, where respiratory motion is a known problem [17]. One strategy to tackle the respiratory motion is to sort the acquired data from both modalities into several gates where no motion is assumed in each of them. The gated data are then paired up according to their breathing phases estimated from the data themselves or an external tracking system [18]. In addition to reconstructing these gated data pairs individually and then registering them to a reference respiratory phase [19], one can also incorporate the corresponding attenuation information into 4-dimensional (4-D) reconstruction algorithms [20], [21]. However, these methods rely on a relatively consistent breathing pattern during both scans [22]. Moreover, they imply the need of special scans to obtain the gated anatomical information. This can increase patient dose or prolong the overall study time, depending on the applied anatomical imaging modality. To adapt to irregular breathing patterns, another strategy applies individual motion model to deform the input attenuation map [23]. The model can be derived from other imaging data, such as dynamic CT and MR [24], as well as the non-attenuation corrected PET [25]. However, the former approach has the potential problem of propagating the error in the model estimation to the final reconstructed image, while the latter method’s performance depends on the tracer distribution...
and data statistics. Another way around these issues is to use population-based deformation models \[26, 27\]. However, these have not been convincingly shown to work in practice \[23\]. The application of applying an individual model to PML image reconstruction using anatomical priors therefore faces similar challenges. Finally, none of the above methods is able to cope with the residual misalignment caused by other general motion of the patient.

Algorithms that allow simultaneous estimation of the activity distribution and the corresponding attenuation map from the respiratory gated PET data have been proposed \[28, 29\] in recent years. These methods do not rely on assumptions about the breathing pattern or a pre-estimated motion model. Therefore, they have the potential to be applied to different misalignment problems without suffering from the error propagation issue. However, since the problem is very ill-conditioned, some a priori knowledge about the intensity distribution of the attenuation map is required. This can compromise the benefit of using anatomical information during the image reconstruction as the intensity is restricted to several values and most of the anatomical details are lost. Besides, significant cross-talk between the estimated activity and attenuation map is observed in non-time-of-flight (non-TOF) PET. Although the artifacts can be largely eliminated when TOF data are available, the a priori knowledge about the intensity distribution is still necessary \[29\].

In contrast to seeking to align the attenuation map with the emission image, a different joint estimation approach incorporates a warp matrix that deforms both the activity distribution and the attenuation map within the objective function \[30–32\]. By optimizing the objective function using an alternating process between motion estimation and image reconstruction, the motion compensation and attenuation correction are achieved simultaneously. The optimization can be applied to both non-TOF and TOF data albeit with a significantly improved convergence rate when TOF data are available \[33\]. The a priori knowledge of the attenuation distribution is not necessary anymore. This study motivated us to investigate the idea of applying a warp matrix to an anatomical prior. Extending on the existing method, two approaches that account for the misalignment between the functional and anatomical images by incorporating the warp matrix into the penalized objective function are proposed. As a special case of the application, we will only investigate the alignment of one PET position with a single CT derived attenuation map, which is also used to provide anatomical information. This paper is an extension of initial results presented in \[34\].

II. METHOD

A. Objective function without considering the potential misalignment

In this section, we define the PML objective function with an anatomical prior without misalignment considerations between the activity and anatomical images. Given the emission image \(f \in \mathbb{R}^J\), the anatomical image \(z \in \mathbb{R}^J\), the attenuation map \(\mu \in \mathbb{R}^J\) and the measured data \(g \in \mathbb{R}^J\), the objective function can be written as:

\[
\Phi(f) = -L(f, g, \mu) + \beta R(f|z),
\]

where \(L\) is the log-likelihood and \(R\) is the penalty function with a parameter \(\beta\) controlling its strength.

As the statistical nature of the measured data \(g\) can be described using the Poisson distribution in emission tomography, the log-likelihood function \(L\), omitting terms independent of \(f\), can be expressed as:

\[
L(f, g, \mu) = \sum g_i \log(\hat{g}_i(f, \mu) - \hat{g}_i(f, \mu)),
\]

\[
\hat{g}(f, \mu) \triangleq \text{diag} \{e^{-A\mu}\} Af + n
\]

(2)

where \(\hat{g}_i\) is the mean measurement in bin \(i\), \(A \in \mathbb{R}^{|J| \times |J|}\) is the system matrix which characterizes the physical system properties, such as resolution and detector sensitivity, in terms of detection probability and \(n \in \mathbb{R}^{|J|}\) is the expected background events vector. The attenuation effect is modeled explicitly by the matrix \(\text{diag} \{e^{-A\mu}\}\), where \(\text{diag} \{\cdot\}\) is an operator that constructs a diagonal matrix from a vector.

Since it has shown promising results in the literature \[12, 35, 36\]. Parallel Level Sets (PLS) is chosen as a representative anatomical penalty in this study:

\[
R(f|z) = \sum_j \sqrt{\epsilon^2 + \|\nabla f\|_2^2 - \langle \nabla f, \xi_j \rangle^2},
\]

\[
\|\xi_j\|_2 := \frac{|\nabla z_j|}{\sqrt{\|\nabla z_j\|_2^2 + \eta^2}} \quad \epsilon \text{ and } \eta > 0
\]

(3)

where \(\nabla\) is the gradient operator, \(\langle \cdot, \cdot \rangle\) is the Euclidean scalar product and \(\| \cdot \|_2\) denotes the \(\ell^2\)-norm. The edge preserving property of PLS is modulated by the pair of parameters \((\epsilon, \eta)\).

B. Objective function considering the potential misalignment

Two approaches that account for the misalignment between the functional and anatomical images in penalized image reconstruction using anatomical priors are proposed in this section. Both approaches are based on a joint motion estimation and image reconstruction method proposed recently for dealing with the mismatch between the attenuation map and the PET image in respiratory gated PET/CT \[30\]. Instead of applying a quadratic penalty function to enforce smoothness on the reconstructed activity images as in \[30\], an anatomical penalty calculated with the attenuation map is employed to improve the image quality. Therefore, artifacts induced by the misalignment between the activity image and the attenuation map will be introduced through both the attenuation correction and the incorporated penalty function. The main difference between these two approaches is that the first approach \(\Phi_1\) (Approach I) deforms the anatomical image (i.e., the attenuation map) to align it with the functional image, while the second approach \(\Phi_2\) (Approach II) deforms both images to align them with the measured data. Although the deformation of the attenuation map changes the shape of the scatter distribution, the estimated background events are fixed during the optimization process for simplicity. As in \[30\],
we use uniform cubic B-splines for image interpolation and deformation. Despite the use of an anatomical prior, Approach II is quite similar to the method introduced in [30] and Approach I is essentially a simplified algorithm to Approach II. We also modified Approach II to impose positivity on image values as opposed to B-spline coefficients.

Assume a continuous volumetric image \( s : \mathbb{R}^3 \rightarrow \mathbb{R} \) can be represented as a linear combination of basis functions centered on a voxel grid \( C = \{ r_k, k = 1, \ldots, N \} \subset \mathbb{R}^3 \) that coincides with the voxel centers:

\[
s(r) = \sum_{k=1}^{N} s'_k B \left( \frac{r - r_k}{\sigma_1} \right),
\]

where \( s'_k \) is the B-spline coefficient of the basis function centered on voxel \( k \), \( r = (x, y, z) \) is the index vector in the 3-D Cartesian coordinate system, \( B(r) = b(x)b(y)b(z) \) is an interpolating function based on the cubic B-splines \( b \) and \( \sigma_1 \) represents the voxel-spacing. The discretized image can therefore be represented as a collection of the B-spline coefficients \( s' = (s'_j)_{j=1}^{N} \). From this section, the prime notation is used to distinguish the B-spline coefficients from the corresponding coefficient vector that accurately corrects their images in order to obtain an estimate that optimizes the log-likelihood \( L \) and the incorporated anatomical penalty \( R \) as both functions use the warped attenuation map \( W^\mu \) as inputs. Since this approach does not require deforming the activity image, \( f \) in \((7)\) represents a vector of image values.

The positivity constraint on \( f \) can therefore be achieved by performing constrained image reconstruction. In contrast, the attenuation map is represented as a collection of coefficients \( \mu' \) for image warping using B-splines. This could lead to negative values in \( W^\mu \) as we are optimizing the B-spline coefficients. However, since small negative values in \( W^\mu \) would become attenuation factors very close to one, they have been left unchanged in this study. When the objective function in \((7)\) is optimized, the warped attenuation map should be in the same space as the activity image and \( e^{-gAW^\mu} \) is a coefficient vector that accurately corrects \( f \) for attenuation in the projection domain. In other words, \( W^\mu \) and \( f \) are aligned and adequately projected to fit the data \( g \).

2) Approach II: Instead of seeking to align the warped attenuation map with the reconstructed activity image, the second approach deforms both the anatomical and functional images in order to obtain an estimate that optimizes the objective function \( \Phi_2 \):

\[
\Phi_2(f', \mu', \theta) = -L(Wf', g, W^\mu) + \beta R(f|f^\mu) + \gamma U(\theta) + \delta E(Wf') \tag{8}
\]

where

\[
E(s) = \sum_{n=1}^{N} \min(0, s(\nu_0(\tilde{r}_n)))^2 \tag{9}
\]

is a barrier function that penalizes negative values in \( Wf' \) \([37] \). Given \( \tilde{C} = \{ \tilde{r}_n, n = 1, \ldots, \tilde{N} \} \) a finer grid that contains a finite number of uniformly spaced locations in each interval of two grid nodes in the voxel grid \( C \), the function computes the spline values (i.e., the image values) centered on the finer grid and penalizes the square of any negatives. The strength of \( E \) is determined by the parameter \( \delta \). In this study, we defined the distance between two adjacent locations in \( \tilde{C} \) equal to one quarter of the grid spacing used for the image.

Although the log-likelihood requires the warped emission and anatomical images as inputs, the penalty function is calculated with the image value of the non-warped ones. Since the motivation of using an anatomical prior is to encourage edges in the emission image corresponding to those in the anatomical one, finding common edges in the warped or non-warped images is essentially a similar optimization problem. In other words, calculating the anatomical penalty function with \( Wf' \) and \( W^\mu \) should lead to (nearly) the same solution.

In summary, when the objective function in \((8)\) is optimized, the emission and anatomical images are aligned such that the attenuation corrected projections calculated with \( Wf' \) and \( W^\mu \) fit the measured data \( g \).

C. Algorithm implementation

In both approaches the optimization was implemented as an alternating process that includes a misalignment estimation.
subroutine and a penalized image reconstruction subroutine. Pseudo-code that summarizes the implementation can be found in Algorithm 1. The workflow was defined by the number of inner iterations (InnerIter1 and InnerIter2 in Algorithm 1) for these two subroutines and the number of outer iterations (OuterIter in Algorithm 1) that controls the repetition of the alternating process. Since limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) based algorithms show the potential to work with a relatively wide range of penalty functions [33], we applied L-BFGS for unconstrained optimization (misalignment estimation in both approaches and image reconstruction in the second approach) and L-BFGS-B [39] for the positivity constrained image reconstruction in Approach I. The statement $x \leftarrow \text{L-BFGS}(G, x_0, Niter)$ in Algorithm 1 means optimizing function $G$ using algorithm L-BFGS with initial point $x_0$ and Niter iterations, where $x$ can be either activity image or deformation coefficients depending on the context. Ordered subsets expectation maximization (OS-EM) was used to reconstruct the initial activity image $f_0$ of the whole process. The misalignment estimation was then initialized by $f_0$ and the attenuation map $\mu$. The implementation of the misalignment estimation employed in this study was originally proposed in [30]. Every time the misalignment estimation was done, a new initial image $f_{\text{initInner}}$ for the penalized image reconstruction was recomputed using OS-EM, taking into account the current estimated misalignment. To improve the convergence rate of the penalized image reconstruction, a preconditioner proposed in [40] was incorporated into both approaches. A spatially-variant penalization scheme was also applied to the anatomical penalty function to further achieve uniform local contrast [38]. Both the preconditioner and the spatially-variant penalty strength were calculated with the initial image from OS-EM at every outer iteration as well.

### III. Evaluation

Since both approaches should be able to find a warped attenuation map that helps maximize the objective function, the evaluation is focused on the performance of the misalignment subroutine of each approach.

#### A. Data

Two XCAT phantoms [41] representing different respiratory phases and the corresponding $\mu$ maps (Figure 1) were produced to simulate different PET positions. Both phantoms were a $128 \times 128 \times 47$ matrix with voxel size of $3.906 \text{ mm}$ in all directions. The set of images at end inspiration was used to generate data similar to that from a GE Discovery STE in 3-D non-TOF acquisition mode. The number of projection angles has been down sampled from 280 to 140 to accelerate the computation. Both approaches were initially evaluated with a noiseless dataset. To further assess their performance in the presence of noise, a dataset with total counts of 161 M was also simulated using the Poisson noise model. Note that all simulations took into account the attenuation effect and system blurring using FWHM = 5.2 mm in tangential and radial directions and 5.7 mm in trans-axial direction. To simulate the misalignment between functional and anatomical images, the attenuation map at end expiration was used as the initial input for both attenuation correction and misalignment estimation.

#### B. Reconstruction

The selection of the strength of each penalty was based on an initial investigation, where the difference between the warped and target $\mu$ maps at OuterIter = 30 was visually compared with respect to a given set of candidate strengths (results not shown). We studied the strength of one penalty at a time using the noiseless dataset and the value from the set giving the best visual alignment was recorded. As a result, for the noiseless dataset, the set of parameters that determines the strength of each penalty function was $(\beta, \gamma) = (7 \times 10^{-3}, 10^{-4})$ for $\Phi_1$ and $(\beta, \gamma, \delta) = (7 \times 10^{-3}, 10^{-4}, 10^{-1})$ for $\Phi_2$. A stronger $\beta = 2 \times 10^{-1}$ was chosen when the data with noise was considered for either approach. The strength of other penalty function(s) remained the same as for the noiseless dataset. The parameter pair $(c, \eta)$ in PLS was fixed at $(10^{-1}, 10^{-2})$. The distance between two grid nodes for the deformation model was 6 voxels. The alternating process

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**Algorithm 1: Pseudo-code for the alternating process**

**Input:** Data $g$, attenuation map $\mu$ and strength of each penalty function (i.e., the set of parameters $(\beta, \gamma)$ for Approach I and $(\beta, \gamma, \delta)$ for Approach II

**Output:** Estimated tracer distribution $f$ and B-spline deformation coefficient $\theta$

```
\begin{algorithm}
\caption{Pseudo-code for the alternating process}
\begin{algorithmic}
\State \textbf{Input:} Data $g$, attenuation map $\mu$ and strength of each penalty function 
\State \textbf{Output:} Estimated tracer distribution $f$ and B-spline deformation coefficient $\theta$
\State $\theta_0 \gets 0$
\State $f_0 \gets \text{OS-EM}(g, \mu, \theta_0)$
\For{$t = 0, \ldots, \text{OuterIter} \ - \ 1$}
  \For{$\text{misalignment estimation}$}
    \If{Approach I}
      \State Define $F: \theta \mapsto \Phi_1(f, \mu, \theta)$
    \Else if Approace II
      \State Define $F: \theta \mapsto \Phi_2(f, \mu, \theta)$
    \EndIf
  \EndFor
  \State $\theta_{t+1} \gets \text{L-BFGS}(F, \theta_t, \text{InnerIter1})$
  \State $f_{\text{initInner}} \gets \text{OS-EM}(g, \mu, \theta_{t+1})$
  \If{Approach I}
    \State Define $H: f \mapsto \Phi_1(f, \mu, \theta_{t+1})$
    \State $f_{\text{InnerIter2}} \gets \text{L-BFGS-B}(H, f_{\text{initInner}}, \text{InnerIter2})$
  \Else if Approace II
    \State Define $H: f \mapsto \Phi_2(f, \mu, \theta_{t+1})$
    \State $f_{\text{InnerIter2}} \gets \text{L-BFGS-B}(H, f_{\text{initInner}}, \text{InnerIter2})$
  \EndIf
  \State $f_{t+1} \gets f_{\text{InnerIter2}}$
\EndFor
\end{algorithmic}
```

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**Fig. 1.** The central coronal view of the XCAT phantoms representing end inspiration (top left) and expiration (top right). The corresponding $\mu$ maps are also provided (bottom).
as well as the image reconstruction subroutine at every outer iteration were initialized by one full iteration of OS-EM with 14 subsets. This initial image was also used for calculating the preconditioner and the spatially-variant penalty strength for the anatomical prior. Up to 100 outer iterations were used for both approaches. Each reconstructed activity image and the warped attenuation map had 128 × 128 × 47 voxels with voxel size of 4.687 × 4.687 × 3.27 mm³.

C. Analysis

The noiseless dataset was initially used to find reasonable settings for the parameters in both approaches. We started with finding the workflow that provides satisfactory results for both approaches such that the performance evaluation was conducted at a given outer iteration with the same number of iterations for each subroutine to investigate whether the use of an anatomical prior is beneficial for either approaches, reconstructions without considering any structural information were performed as well. This was achieved by substituting the anatomical image (i.e., μ map at end expiration) with a uniform image when calculating PLS, therefore it is equivalent to using a (smooth) total variation (TV) prior. The difference image between the warped and target μ maps at a given outer iteration was used to evaluate the performance of misalignment estimation. As the lungs are the main target of the respiratory motion alignment, a mask was applied to the difference images and the root-mean-square errors (RMSE) was computed in the lungs to reflect the misalignment estimation of small structures of the lungs. The RMSE in the lungs was then plotted against the outer iteration numbers to quantify the performance.

A two-part study was conducted to find the workflow in common for both approaches. In the first part of the study, we used 1 inner iteration for the misalignment estimation and explored the minimum iterations required for the image reconstruction subroutine to obtain satisfactory results. The studied inner iteration numbers for the image reconstruction subroutine (InnerIter2) were 1, 5, 10 and 20. We then fixed the iteration number for the image reconstruction to the limit found in the first part and increased the number of iterations for the misalignment estimation (InnerIter1) from 1 to 5, 15 or 30 to assess if the performance of the misalignment estimation can be improved by using a higher inner iteration number. The number of outer iterations that controls the repetition of the alternating process was fixed at 100 (OuterIter = 100) such that the workflow was determined by the selected inner iteration number for each subroutine to reduce the number of parameters to investigate.

The workflow giving satisfactory results for both approaches found with the noiseless dataset was then further investigated on the noisy dataset. Recall that a stronger strength β = 2 × 10⁻¹ was used for the anatomical penalty function in the presence of noise. As the convergence rate of the preconditioned L-BFGS-B (L-BFGS-B-PC) varies with the strength of the penalty function and data noise level [40], the alternating process was also performed with a higher InnerIter2 = 20 or 40 for both approaches for the noisy dataset. The number of inner iterations for the misalignment subroutine was kept the same as well as the number of outer iterations.

IV. RESULTS

A. Workflow optimization

For the sub-study where the inner iteration number for the misalignment estimation was fixed at 1, the central coronal view of the difference images between the warped and target μ maps at OuterIter = 100 are shown in Figure 2. For both approaches, using InnerIter2 = 1 was problematic, resulting in severe distortion of structures in the warped μ map (Figure 2, top row). Satisfactory results were obtained with Approach I when InnerIter2 = 5 or 10 was chosen (Figure 2, left column, second and third rows). However, when a higher InnerIter2 = 20 was applied, the misalignment around the diaphragm (Figure 2, left column, bottom row) was still observed after 100 outer iterations. In contrast to Approach I, the performance of the misalignment estimation of Approach II was improved as InnerIter2 increased (Figure 2 right column). When InnerIter2 ≥ 10 was used, the algorithm was able to realign the input μ map to the target one at OuterIter = 100.

The RMSE in the lungs was consistent with the visual observation from the difference images. As shown in Figure 3 for both approaches, at OuterIter = 100, the RMSE in the lungs reached the highest error when InnerIter2 = 1 was used. For Approach I, the optimal InnerIter2 was 5, while the RMSE in the lungs decreased as InnerIter2 increased for Approach II. In terms of the convergence rate, Approach II was able to reach a relatively stable RMSE in the lungs after 60 outer iterations. In contrast, Approach I did not yet reach a stable RMSE in the lungs at 100 outer iterations for all evaluated workflows.

Since both approaches provided visually and numerically good results when InnerIter2 = 10 was used, we fixed InnerIter2 = 10 and increased the iteration number used in the misalignment estimation subroutine. Figure 4 shows the central coronal view of the difference image between the warped and target μ maps for both approaches with various InnerIter1 and a fixed InnerIter2 = 10. The misalignment around the diaphragm region became apparent for Approach I at OuterIter = 100 as InnerIter1 > 1 was chosen (Figure 4 left column). For Approach II, however, the difference images
Note that the anatomical information was utilized throughout the workflow optimization study. The corresponding central coronal view of the reconstructed images at OuterIter = 100 were visually identical, regardless of the number of the applied InnerIter1 (Figure 4, right column).

The RMSE in the lungs for Approach I and II with different InnerIter1 plotted against the outer iteration numbers are given in Figure 5. Consistent with the visual comparison, for the first approach, the smallest RMSE in the lungs at OuterIter = 100 was achieved by the workflow with InnerIter1 = 1. When Approach II was adopted, all workflows with different InnerIter1 settings were able to achieve a similar RMSE in the lungs at OuterIter = 100. The convergence rate of the misalignment estimation of Approach II was improved as InnerIter1 increased. However, the performance of Approach I in terms of the convergence rate of the RMSE in the lungs seemed insensitive to the change of the inner iteration number for the misalignment estimation when the applied InnerIter1 was larger than 1.

Based on the results shown in this section, 1 iteration of misalignment estimation (InnerIter1 = 1), followed by 10 iterations of image reconstruction (InnerIter2 = 10) was defined as the workflow that provides satisfactory results for these two approaches when the noiseless dataset is considered. The corresponding central coronal view of the reconstructed functional images at OuterIter = 100 are provided in Figure 6. Note that the anatomical information was utilized throughout the workflow optimization study.

### B. Influence of incorporating anatomical priors on misalignment estimation

As observed in the central coronal view of the difference images at 100 outer iterations (Figure 7 and 8, bottom row), both Approach I and II were able to estimate the misalignment and warp the input attenuation map accordingly, regardless of the presence of the anatomical information. However, in terms of the convergence rate, these two approaches had different responses to the use of the anatomical information. For the first approach, incorporating the anatomical information degraded the convergence rate of the misalignment estimation. The central coronal view of the difference images at OuterIter = 20 and 60 for the reconstructions without using anatomical information showed less apparent misalignment around the diaphragm region compared to those for the reconstructions considering the anatomical information (Figure 4, top and second rows). In contrast, Approach II was able to achieve a faster convergence rate when the additional anatomical information was available (Figure 8, top and second rows). These observations were further demonstrated by the RMSE in the lungs plotted against the outer iteration numbers (Figure 9). When the anatomical information was considered, Approach II reached a stable RMSE in the lungs after around 60 outer iterations, while Approach I required more than 80 outer iterations to achieve that.

### C. Preliminary investigation on noisy data

Figure 10 shows the central coronal view of the difference image between the warped and target $\mu'$ maps for each reconstruction condition at OuterIter = 100. As observed in the figure, the first approach still suffered from the misalignment issue at 100 outer iteration when InnerIter2 = 10 or 20 were applied (Figure 10, left column, top and second images). Consistent with the results for the noiseless dataset (Figure 2), the performance of the misalignment estimation
of the second approach was less sensitive to the applied number of InnerIter2. Note that the alignment of the contour of the object was improved as InnerIter2 increased for both approaches. The RMSE in the lungs plotted against the outer iteration numbers support our observations from the difference images (Figure 11). Moreover, Approach II converged faster than Approach I for all evaluated workflows. The corresponding reconstructed functional images for InnerIter2 = 40 are provided in Figure 12.

V. DISCUSSION

The potential misalignment between functional and anatomical images is the main concern for incorporating an anatomical prior into image reconstruction. Expanding on the algorithm proposed in [30], two approaches that perform alternating misalignment estimation and penalized image reconstruction using anatomical priors are proposed. In this study, we focused on the performance of the misalignment estimation of each approach for the thorax with one gate of non-TOF PET data in which no motion was assumed. The \( \mu \) map was used for attenuation correction and anatomical prior calculation. Therefore, misalignment will affect both factors, with subsequent influence on the optimization. Both approaches have shown the ability to estimate the misalignment and warp the anatomical image accordingly, but with a different convergence rate, depending on the applied workflow and if the anatomical information is included as a prior.

To study how the change of the workflow and the presence of anatomical information influence the performance of the proposed approaches, initial evaluations on noiseless datasets were conducted. As the maximum outer iteration number that controls the repetition of the alternating process was set to 100,
the workflow of both approaches was determined by the number of iterations for the misalignment estimation (InnerIter1) and image reconstruction (InnerIter2) subroutines. Based on the results shown in Section IV-A when a sufficient number of image reconstruction subroutine was applied, Approach II showed the ability to achieve a good alignment in less outer iterations compared to Approach I. Its performance was also less sensitive to the change of workflow. The use of a larger InnerIter1 or InnerIter2 improved the convergence rate of the misalignment estimation for Approach II but slowed it down for Approach I. For the given workflow with InnerIter1 = 1 and InnerIter2 = 10, Approach II required a larger outer iteration to achieve a good result (Figure 8) in the case where the anatomical information was absent. However, the convergence rate of misalignment estimation was improved for Approach I when the anatomical information was not available (Figure 7).

The workflow suggested in Section IV-A for the noiseless data was further investigated on one noisy dataset. Based on the result shown in Figure 10, both approaches required a higher number of iterations for the image reconstruction subroutine to achieve good results in 100 outer iterations. Since the strength of the anatomical penalty function was increased in order to regularize noise as well, it is hard to attribute the cause to the presence of noise or the change of penalty strength. The observation also implies that the required number of InnerIter2 should be optimized according to these factors. Although further investigation on data representing different noise levels and reconstructed with different conditions is necessary, we found that using the workflow with InnerIter1 = 1 and InnerIter2 = 40 should be sufficient for all simulations applying either approach in this study. Consistent with results for the noiseless dataset, Approach II showed lower sensitivity to the change of workflow and outperformed Approach I in terms of the convergence rate of misalignment estimation (Figure 11). For all evaluated workflows with different numbers of InnerIter2, it was able to achieve a stable RMSE in the lungs in less outer iterations.

In this study, a workflow (1 iteration of misalignment estimation, followed by 10 iterations of image reconstruction) that gave good results for both approaches was sought to be able to compare their performance. Further improvement in convergence rate can be expected by optimizing the workflow specifically for each approach. Since one iteration of motion estimation is computationally more expensive than one iteration of image reconstruction, a measure that reflects the computational demand of each approach is therefore required.

For both approaches, the strength of each penalty function was chosen based on the performance of the misalignment estimation. However, together with the implied interpolation of image warping and re-sampling using B-splines, the selected penalty strengths led to over-regularized functional images. This could be overcome by running a final image reconstruction incorporating warping with settings optimized for the estimation of the functional image. It remains to be investigated if the introduction of the anatomical prior would introduce errors in the alignment estimation for cases where edges in functional and anatomical images are not consistent.

Since the deformation of the attenuation map is likely to lead to a different scatter distribution, the estimated background events should be updated accordingly during the optimization. However, the effect was assumed to be small and ignored for simplicity in the current study. To achieve accurate quantification, performing active scatter correction based on the update of the estimated activity distribution might be necessary. In practice, this could be done by re-estimating the scatter after a number of iterations of the current algorithm.

In the current study, we have adapted the strategy often used in CT or MR derived attenuation correction that downsamples the anatomical image to match the resolution of PET and surrenders the structural details carried by the high-resolution anatomical image. However, it could be beneficial to reconstruct the PET image at the same voxel size as the anatomical image instead [42]. The benefit of using TOF data for misalignment estimation was studied in [33] where a similar algorithm was applied to obtain reconstructed activity images with aligned attenuation correction. As Approach I and II are extensions of that algorithm, practical convergence of misalignment estimation in less outer iterations can be expected when TOF data are available.

The algorithms proposed in this study have been demonstrated with simulation. A thorough validation with more realistic data is required to demonstrate usefulness in future applications in the clinic. In addition, as the algorithm performance and the quantitative accuracy can be affected by the penalty strength and other parameters that determine the edge-preserving property of the penalty (e.g., ϵ and η in PLS), future work should also include parameter optimization with respect to different applications. To investigate the effectiveness of applying the proposed approaches in improving quantitative accuracy, evaluations using phantoms with inserted features or patient datasets with pseudo-lesions should also be included. In our current work, we assumed that the attenuation correction and anatomical image used for PLS were the same. However, the algorithms can be generalized to other user cases where the anatomical image is independent of the attenuation image. One particular case of this might be reconstructions of PET/CT data using an anatomical prior derived from MR images.

As in [30], we have chosen to use the uniform cubic B-splines to model the image deformation. As no priori knowledge regarding the misalignment is required, it should be able to adapt to various misalignment scenarios caused by different types of motion effect. However, due to the implied interpolation, it also leads to a smooth deformation field which will not be able to accurately model sliding motion such as occurs between the lung and ribcage. To improve the accuracy of the misalignment estimation and make maximum use of the anatomical information, the investigation of other differentiable deformation models specific to different applications should be included in future work. However, as long as the deformation field can be parametrizable using a linear sum of basis-functions, the methods described here would be applicable.

**VI. Conclusions**

Two approaches for solving the potential misalignment between the functional and anatomical images in penalized
image reconstruction using anatomical priors have been proposed in this study. The main difference between them is that the first approach deforms the anatomical image to align it with the functional one, while the second approach deforms both images to align them with the measured data. Both approaches were implemented using alternation between misalignment estimation and image reconstruction. The results demonstrated that both methods are able to estimate the misalignment and deform the anatomical image when a proper workflow for the alternating optimization is applied. Moreover, the second approach shows the ability to converge to the correct alignment faster than the first approach and is less sensitive to variations in the workflow. The use of anatomical information improves the convergence rate of misalignment estimation for the second approach, although slowed it down for the first approach. These encouraging results indicate that it is possible to align functional and anatomical information, overcoming a serious limitation in practical use of anatomical priors.

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