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A biomechanical modeling-guided simultaneous motion estimation and image reconstruction technique (SMEIR-Bio) for 4D-CBCT reconstruction

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Abstract

Reconstructing four-dimensional cone-beam computed tomography (4D-CBCT) images directly from respiratory phase-sorted traditional 3D-CBCT projections can capture target motion trajectory, reduce motion artifacts, and reduce imaging dose and time. However, the limited numbers of projections in each phase after phase-sorting decreases CBCT image quality under traditional reconstruction techniques. To address this problem, we developed a simultaneous motion estimation and image reconstruction (SMEIR) algorithm, an iterative method that can reconstruct higher quality 4D-CBCT images from limited projections using an inter-phase intensity-driven motion model. However, the accuracy of the intensity-driven motion model is limited in regions with fine details whose quality is degraded due to insufficient projection number, which consequently degrades the reconstructed image quality in corresponding regions. In this study, we developed a new 4D-CBCT reconstruction algorithm by introducing biomechanical modeling into SMEIR (SMEIR-Bio) to boost the accuracy of the motion model in regions with small fine structures. The biomechanical modeling uses tetrahedral meshes to model organs of interest and solves internal organ motion using tissue elasticity parameters and mesh boundary conditions. This physics-driven approach enhances the accuracy of solved motion in the organ's fine structures regions. This study used 11 lung patient cases to evaluate the performance of SMEIR-Bio, making both qualitative and quantitative comparisons between SMEIR-Bio, SMEIR, and the algebraic reconstruction technique with total variation regularization (ART-TV). The reconstruction results suggest that SMEIR-Bio improves the motion model's accuracy in regions containing small fine details, which consequently enhances the accuracy and quality of the reconstructed 4D-CBCT images.

Keywords

4D-CBCT; SMEIR; Lung; Biomechanical Modeling; Mooney-Rivlin Material

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1. INTRODUCTION

Linear accelerator-integrated cone-beam computed tomography (CBCT) is widely used to acquire high-resolution three-dimensional (3D) anatomical images for image-guided radiation therapy (IGRT). However, when applied to sites that involve motion (such as the lungs), acquired 3D-CBCT images contain respiratory motion artifacts such as blurring, streaking, and distortion, which affect the feasibility and accuracy of IGRT. Respiratory correlated CBCT [1], also called four-dimensional (4D) CBCT, has been developed to acquire phase-resolved volumetric images that minimize motion artifacts. 4D-CBCT groups projections acquired in the same phase from each respiratory cycle together to reconstruct a phase image. These phase-sorted projections contain minimal intra-phase motion, which substantially removes the motion artifacts from the reconstructed image. Subsequently, a series of phase-resolved 3D volumetric images can be stacked together to track the anatomical structures' motion trajectory.

4D-CBCT imaging usually needs to acquire more projections than traditional 3D-CBCT, so it requires more scan time and a higher imaging dose [2]. Ideally, using sorted traditional 3D-CBCT scan projections to reconstruct a high-quality 4D-CBCT image would achieve a short scanning time and low imaging dose, but it does so at the cost of undersampling of each phase. Conventional analytical Feldkamp-Davis-Kress (FDK) reconstruction algorithm [3], which is widely used in the clinic for CBCT reconstruction, generates images with severe streak artifacts from undersampled projections [1]. To improve the quality of image reconstruction, many iterative techniques have been developed [4–7]. These algorithms solve the reconstruction problem by iteratively matching the forward projections of the reconstructed image to the actually acquired projections. These techniques usually also include sparsifying transformations, such as total variation minimization [4, 5] and nonlocal mean regularization [7], in the objective function to optimize the reconstructed image. These iterative methods can greatly improve image quality compared to FDK reconstruction. However, most of these methods reconstruct CBCT images at each phase independently. When few projections exist in each respiratory phase, the reconstructed images may suffer from over-smoothing issues caused by information-lacking regularization.

In addition to the information provided by sorted projections of each phase, the correlations between different respiratory phases may help to improve the 4D-CBCT reconstruction quality [8]. Motion-compensated CBCT reconstruction algorithms have been proposed that combine the information from all phases to reconstruct a single motion-suppressed reference phase image using an inter-phase motion model [9–11]. Combining information from all phases, the motion-suppressed reconstruction technique outputs higher quality images than images reconstructed using projections from a single phase alone. However, the inter-phase motion model is extracted by registering between the reconstructed low-quality CBCT phase images, whose accuracy is susceptible to the artifacts present in these images [9]. Other methods try to extract motion models from prior 4D-CT images with the assumption that the respiration patterns of 4D-CT and 4D-CBCT are similar; these methods' accuracy can be affected by the motion pattern variations and anatomical changes between CT and CBCT acquisition [10–13]. Methods have also been developed to resolve motion between prior 4D-

CT/CBCT and new 4D-CT/CBCT images using 2D–3D deformation, but these methods rely on a high-quality prior CT/CBCT imaging set that may not always exist [6, 14, 15].

Recently, we developed a simultaneous motion estimation and image reconstruction (SMEIR) technique for 4D-CBCT reconstruction [16]. SMEIR uses an inter-phase motion model to combine projections of all phases to reconstruct a reference phase image. The inter-phase motion is represented as deformation vector fields (DVs) between the reference phase image and all other phase images. Specifically, SMEIR is composed of two steps: the motion-compensated reconstruction step and the motion estimation step. The first step uses a motion-compensated simultaneous algebraic reconstruction technique (MC-SART) to reconstruct a reference image using projections of all phases and the inter-phase DVs [16]. The motion estimation step uses inverse consistent 2D–3D deformable registration to update the DVs between the reference phase and the other phases [16, 17]. The DVs are iteratively updated during the SMEIR optimization, so their qualities and accuracies continuously improve without being constrained by the initial quality of the reconstructed CBCT phase images. However, 2D–3D deformation updates the DVs based solely on image intensity matching. These DVs achieve high accuracy at lung boundary regions, but they suffer from limited accuracy in regions which contain small fine details. Accordingly, the accuracy of reconstructed CBCT images at these regions is limited.

This study developed a biomechanical modeling-guided SMEIR technique (SMEIR-Bio) to improve motion model accuracy in regions with small fine details whose reconstruction quality is degraded by limited projections at each phase. Biomechanical modeling has been proposed recently to solve deformation problems based on tissue composition and their corresponding elasticity properties, rather than on image intensity matching [18–27]. Therefore, biomechanical modeling can improve motion accuracy in regions with limited intensity variations. By applying appropriate boundary conditions, computational mechanical models enable the derivation of physiological and physical organ behaviors in the form of intra-organ deformation vector fields (DVs) by finite element analysis. Therefore, the DVs generated by SMEIR-Bio, combined with biomechanical modeling, can be more biomechanically realistic and accurate in regions with small, fine structures, which can also boost the accuracy of reconstructed 4D-CBCT images.

We evaluated this method with 4D-CT data from 11 lung cancer patients. We simulated 4D-CBCT projections from the 4D-CT images and used them for reconstruction. We made quantitative comparisons between images reconstructed by different methods and evaluated the DVs' accuracy. This method can offer detailed information inside lung with high accuracy which can offer high quality geometric anatomy and benefit for IGRT.

2. METHODS AND MATERIALS

2.1 Methods

SMEIR-Bio is a reconstruction algorithm that iterates and alternates between motion-compensated reconstruction, intensity-driven motion estimation, and biomechanical modeling-guided motion fine-tuning. Detailed descriptions of each key component and the entire workflow follow below.

2.1.1 Motion-compensated reconstruction—In this study, deformation vector fields (DVF), which deform volumetric images through trilinear interpolation, represent the motion model between different 4D-CBCT phases [15, 16]. Motion-compensated reconstruction uses these DVFs to deform images of other phases into a single reference phase, effectively combining all projection information to resolve the undersampling that results from phase-sorting. We selected the end-expiration phase (phase 0) as the reference phase because of its relative stability [28]. We applied the motion-compensated simultaneous algebraic reconstruction technique (MC-SART), which combines projections from all respiratory phases, to reconstruct the reference phase image. This reference phase image can be deformed to other phases using the backward DVFs [16], as shown in Eq. 1 and Eq. 2.

$$\mu_j^{0,(k+1)} = \mu_j^{0,(k)} + \lambda \frac{\sum_{t,n} d_{jn}^{t \rightarrow 0} \sum_i \left[a_{in} \frac{p_i^t - \sum_n a_{in} \mu_n^{t,(k)}}{\sum_{n=1}^j a_{in}} \right]}{\sum_{t,n} d_{jn}^{t \rightarrow 0} \sum_i a_{in}} \quad (1)$$

$$\mu_n^{t,(k)} = \sum_j d_{jn}^{0 \rightarrow t} \mu_j^{0,(k)} \quad (2)$$

μ^0 denotes the voxel-wise attenuation coefficients of the CBCT volume at the reference phase 0. μ^t denotes the corresponding attenuation coefficients at phase t . j and n denote the voxel coordinates for μ^0 and μ^t , respectively. k denotes the iteration number. a_{in} represents the elements of the forward projection matrix along projection line i . p_i^t represents the projection integral value at corresponding pixel i for phase t . $d_{jn}^{t \rightarrow 0}$ denotes the elements of the voxel-wise forward deformation vector field from phase t to phase 0. $d_{jn}^{0 \rightarrow t}$ denotes the elements of the voxel-wise backward deformation vector field from phase 0 to phase t (Eq. 2).

In Eq. 1, the term $p_i^t - \sum_n a_{in} \mu_n^{t,(k)}$ calculates the mismatch between the actual acquired projection of phase t and the forward projection of the reconstructed image at phase t by ray-tracing [29]. Then, the projection-domain mismatch is back-projected into the 3D volumetric image domain. The deformation vector field $d_{jn}^{t \rightarrow 0}$ deforms the error image of phase t to add to the reference phase image for correction. For each phase image t , $d_{jn}^{t \rightarrow 0}$ applies the deformation vector fields to deform the n th voxel at phase t onto the j th voxel at the reference phase. For each phase t , there may be more than one voxel that could be deformed to the j th voxel in the reference phase image. Therefore, a summation of n is required. By applying corresponding DVFs, information from all phases is combined to reconstruct and fine-tune the reference phase image. The reconstruction results depend on the accuracy of the inter-phase DVFs, which necessitates DVF optimization by motion estimation. The relaxation factor λ in Eq. 1 is set to 1. The same value has been used in our previous publications [16, 30], which balances the speed of convergence and the reconstruction noise.

The same λ value has been used throughout the SMEIR-Bio algorithm. The motion-compensated SART reconstruction is followed by total variation regularization of the image to reduce artifacts and noise. The TV minimization uses a standard gradient descent approach with 10 iterations in our study.

2.1.2 Motion estimation—For motion estimation, an inverse-consistent 2D–3D registration algorithm is applied to solve $d_{jn}^{t \rightarrow 0}$ and $d_{jn}^{0 \rightarrow t}$ simultaneously. By minimizing the cost functions $f_1(D^{0 \rightarrow t})$ and $f_2(D^{t \rightarrow 0})$, the DVFs can be solved. f_1 and f_2 are defined as below:

$$f_1(D^{0 \rightarrow t}) = \|p^t - A\mu^0(x + D^{0 \rightarrow t})\|_{l_2}^2 + \beta\phi(D^{0 \rightarrow t}) \quad (3)$$

$$f_2(D^{t \rightarrow 0}) = \|p^0 - A\mu^t(x + D^{t \rightarrow 0})\|_{l_2}^2 + \beta\phi(D^{t \rightarrow 0}) \quad (4)$$

A denotes the projection system matrix. x denotes the coordinate grids of the volumetric image. $D^{t \rightarrow 0}$ denotes the forward DVF matrix, and $D^{0 \rightarrow t}$ denotes the backward DVF matrix. $d_{jn}^{0 \rightarrow t}$ in Eq. 1 makes the element of $D^{0 \rightarrow t}$, and $d_{jn}^{t \rightarrow 0}$ makes the element of $D^{t \rightarrow 0}$. The first term on the right side of each equation denotes the data fidelity term, which measures the differences between the acquired projections and the computed projections of the deformed CBCT volume. The second term on the right side denotes an energy function that regularizes the smoothness of DVFs, which promotes faster and more stable convergence [16]. The parameter β is set to 0.05, a value applied in previous 2D–3D deformation studies [16, 30, 31].

D is a matrix of additive displacements. Each element of D denotes one deformation vector containing the displacement of voxel along x (lateral), y (sagittal) and z (caudal) directions between two phases. D can be decomposed into 3 matrices denoting displacement along these three spatial directions individually: D_x , D_y and D_z .

Based on D_x , D_y , and D_z , the relationship between two phase images (μ^0 and μ^t) can be described as following:

$$\mu^0(i, j, k) = \mu^t(i + D_x^{t \rightarrow 0}(i, j, k), j + D_y^{t \rightarrow 0}(i, j, k), k + D_z^{t \rightarrow 0}(i, j, k)) \quad (5)$$

The symbols i , j , k denote the voxel coordinates along the three spatial directions x , y and z .

We formulate the solution of the DVF motion model as an optimization problem to minimize the objective functions f_1 and f_2 . The solution of the DVF is also subject to the inverse consistency constraint defined in Eq. 6 and Eq. 7.

$$D^{0 \rightarrow t} \circ D^{t \rightarrow 0} = 0 = D^{t \rightarrow 0} \circ D^{0 \rightarrow t} \quad (6)$$

$$D^{0 \rightarrow t} \circ D^{t \rightarrow 0} = D^{0 \rightarrow t}(x + D^{t \rightarrow 0}) + D^{t \rightarrow 0} \quad (7)$$

The Eq. 7 defines the composition scheme of forward and backward deformation fields, which should result in zero displacement (Eq. 6). Eq. 6 also ensures the inverse consistency of the deformation, as the composition from either direction should result in zero displacement. Based on Eq. 6, we can solve the forward or the backward deformation field using the available counterpart from either f_1 or f_2 minimization. The same DVF inversion scheme is applied in reference [32]. We applied a nonlinear conjugate gradient algorithm to minimize f_1 and f_2 alternately. The updated $D^{t \rightarrow 0}$ from minimizing f_2 is inverted and input into f_1 as the initial start to update $D^{0 \rightarrow t}$. The updated $D^{0 \rightarrow t}$ is inverted and subsequently fed back into f_2 to update $D^{t \rightarrow 0}$. In total, we apply 10 iterations to optimize $D^{t \rightarrow 0}$ and $D^{0 \rightarrow t}$ in an interleaved fashion. More details on the non-linear conjugate gradient algorithm, together with the corresponding parameters, can be found in the pseudo codes provided in our previous publication [16].

The projection intensity matching-based data fidelity term in the objective function plays an essential role in optimizing the DVFs, as shown in Eq. 3 and Eq. 4. Accordingly, the solved DVFs will be accurate in high-contrast image regions with large intensity variations. However, the DVF accuracy will be limited in low-contrast image areas or areas with small fine structures, both of which suffer from insufficient intensity differences on 2D projections. For lung, the small fine anatomical details are submerged and smeared in 2D projections although they can be fairly easily visualized in appropriate lung windows in the 3D image. This is the reason why we consider the contrast inside of lung within a projection image is low. In the motion estimation step, we are trying to match the projections simulated from a deformed CBCT and actual measured projections (Eq. 3 and Eq. 4). As the contrast within lung is low on a projection image, this will limit the DVF estimation accuracy when we rely on projection intensity difference only. As a result, the reconstruction accuracy of these areas suffers from inaccurate DVFs in the corresponding regions.

2.1.3 Biomechanical modeling—To boost intra-lung DVF accuracy, we introduce biomechanical modeling into the SMEIR algorithm. Biomechanical modeling is a physics-driven deformation approach that can correct and fine-tune the deformation in regions with small fine details by using boundary conditions defined at high-contrast organ surfaces through finite element analysis. To perform this analysis, an organ mesh composed of finite elements must be constructed with a corresponding material model. In this study, we use the hyper-elastic Mooney-Rivlin material model to describe the lung. This model is often applied to biological tissues with large deformations [33, 34]. The strain energy density function of the Mooney-Rivlin model is shown in Eq. 8:

$$W=c_{10}(I_1-3)+c_{01}(I_2-3)+\frac{1}{2}*k(J-1)^2 \quad (8)$$

The first two terms on the right side of Eq. 8 denote the strain energy needed to deform the shape without changing the volume. The third term on the right denotes the strain energy needed to change the volume without altering the shape. I_1 and I_2 are the first and second invariants, respectively, of the right Cauchy-Green deformation tensor. J is the volume ratio [35]. k represents the bulk modulus. c_{10} and c_{01} are coefficients that represent material elastic properties.

Note that the biomechanical modeling can be generally applied to all organs to improve their intra-DVF accuracy. In this study, we focus on modeling the lung for 4D-CBCT reconstruction. To apply biomechanical modeling, the lung is first segmented out from the reference phase image. The segmentation accuracy also affects the boundary condition extracted from the 2D–3D deformation. The lung boundary's high contrast makes it easy to segment by an automatic segmentation technique. For other organs with less clear boundaries (such as the prostate or kidney), automatic segmentation accuracy might be limited, which may require manual correction or more advanced segmentation techniques [36–38]. In our work, auto-segmentation based on the “snake” [39] algorithm is used to generate lung segmentation.

Biomechanical modeling requires lung segmentation to build a tetrahedral mesh model. To evaluate the effects on SMEIR-Bio reconstruction by segmentation differences, we used the ITK-SNAP [40] software package to generate lung segmentations using different methods. There are 4 segmentation methods provided in the ITK-SNAP software, including thresholding, edge-attraction, clustering and classification. We used these 4 methods to generate 4 different lung segmentations and put them into the SMEIR-Bio workflow for image reconstruction. Specifically for this evaluation, we used the lung masks generated from the reference images reconstructed by the 1st iteration of SMEIR-Bio, and did not further update the lung mask during the optimization. Thus the lung masks also contained errors not corrected in the following iterations, which also served the purpose to evaluate how the segmentation errors might affect the reconstruction accuracy of SMEIR-Bio.

Based on this lung segmentation, a lung surface meshed with triangle elements is generated using the open-source Iso2Mesh package [41]. From the meshed lung surface, 3D tetrahedral elements are further generated to cover and model the full lung volume. The boundary condition, defined as the DVF at the lung mesh surface nodes, can thus be applied to solve intra-lung motion through finite element analysis and the Mooney-Rivlin energy density function. We used the open-source FEBio package in this study to solve the finite element analysis [42].

2.1.4 General workflow of SMEIR-Bio—Figure 1 shows the general workflow of SMEIR-Bio. To estimate an initial motion model between the phase images, we use the total variation-regularized algebraic reconstruction technique (ART-TV) [31] to reconstruct a coarse 4D-CBCT set. Then, we perform demons registration [43] to obtain the initial

deformation vector fields (DVs) between the reconstructed reference phase (phase 0) image and all other phase images. We then input the initial DVs, the coarse 4D-CBCT set, and the projections of all phases into the motion-compensation step to update the reference phase image. Based on the updated reference image, we perform motion estimation to update the inter-phase DVs. Before biomechanical modeling, we automatically segment the lung volume out from the reference phase image to generate a tetrahedral mesh model and use the lung surface DVs solved by motion estimation at each phase as the boundary condition for finite element analysis. We then input the biomechanically-corrected DVs into a motion-compensated reconstruction step and assess the reconstruction results for convergence. If not converged, the reconstruction circles back to the motion estimation step, followed by biomechanical modeling and motion-compensated reconstruction until final convergence is achieved.

2.2 Evaluations

2.2.1 Materials—We evaluated the performance of the SMEIR-Bio algorithm on 11 lung cancer patients. We simulated 4D cone-beam projections from a 4D-CT set of each patient for reconstruction. The image size is 256×256 for each patient and the slices number varies between different patients from 190 to 270. And the voxel size is $1.5 \text{ mm} \times 1.5 \text{ mm}$ and the slice thickness is 2 mm. The respiratory rate is around 15 breathings per minute. For the simulation algorithm, we used the ray-tracing technique [29]. We did not add additional noise or scatter in the simulated projections, where only residue artifacts (noise, scatter, beam hardening) in the 4D-CT were considered. For each patient, we generated 4 groups of 4D-CBCT projections to simulate different acquisition sparseness, with 10, 20, 30, or 40 projections per phase. The 4D CBCT projections were simulated from the 4D CT images with 300×250 pixels in each projection. Each pixel measures $2 \text{ mm} \times 2 \text{ mm}$. The simulated source-to-axis distance is 1000 mm, and the source-to-imager distance is set at 1500 mm. Since the projections were simulated from each phase, the acquisition rate and respiration rate were irrelevant. The simulated projections of each phase are evenly distributed across a 360° scan angle. In total, 872 landmarks from all patients identified by expert radiation oncologists were used to verify motion model accuracy.

To further evaluate this method, we take real projections that contain scatter, noise and beam hardening into the consideration. The 4D-CBCT projections were scanned using a Varian Trilogy LINAC (Varian Medical Systems, Palo Alto, CA), with 120 kV peak voltage, and 80 mA/25 ms exposure for each projection. The distance between the x-ray source and the flat panel detector is 1500 mm while the source-to-isocenter distance is 1000 mm. The acquired angular range is $[-265^\circ, -75^\circ]$. The scanning duration is 4.5 min and the average patient breathing cycle is 2.78 s. The 4D-CBCT set has 1982 projections in total, which has been sorted into 10 respiratory phases. Each phase was reconstructed using the ART-TV algorithm and the reconstructed images were used as “gold-standard” reference image. The reconstructed image size is $200 \times 200 \times 100$ and the image resolution is 2 mm. We then downsampled the number of projections at each phase by a factor of 10 to around 20 and performed the SMEIR and SMEIR-Bio reconstructions separately based on the sparse projections.

2.2.2 Biomechanical parameter optimization—The specified elasticity parameters K , c_{10} , and c_{01} , represent the biomechanical features of the lung material, as shown in Eq. 8. c_{10} and c_{01} denotes shear modulus and K denotes bulk modulus. The shear modulus determines the resistance of shape change and the bulk modulus determines the resistance of volume change. Their values will affect the solved intra-lung DVFs under the same boundary condition. The K , c_{10} , and c_{01} are related to Poisson's ratio (ν_p) as shown in Eq. 9:

$$\frac{K}{c_{10} + c_{01}} = \frac{4(1 + \nu_p)}{3(1 - 2\nu_p)} \quad (9)$$

In this study, we set $c_{10} = c_{01} = c$ to simplify the problem. The relationship shown in Eq. 9 can thus be represented as Eq. 10:

$$\frac{K}{c} = \frac{8(1 + \nu_p)}{3(1 - 2\nu_p)} \quad (10)$$

ν_p is Poisson's ratio of material [44] defined as the ratio of lateral contraction to longitudinal extension when a bar is pulled out. It is a dimensionless parameter which is related to the

compressibility of materials[45]. In the Mooney-Rivlin model, the ratio $\frac{k}{c}$ defined in Eq. 10 describes the incompressibility of materials, or the k_factor , which is directly related to Poisson's ratio (ν_p). Previous studies on lung modeling have used a range of Poisson's ratios [19, 23, 25, 46, 47] (Table 1).

We process a k_factor evaluation to find the appropriate k_factor used in the SMEIR-Bio reconstruction. As it is shown in the Eq. 10, the k_factor is calculated from material's Poisson's ratio and will increase with increasing Poisson's ratio. The isotropic lower limit of Poisson's ratio is -1 and the upper limit is 0.5 [48]. The incompressibility of materials increases with Poisson's ratio. When Poisson's ratio reaches 0.5 , it means the material is not compressible and the corresponding k_factor is infinite. Previous studies in Table 1 give a rough range to describe the Poisson's ratio of lung tissue from 0.4 ($k_factor=19$) to 0.499 ($k_factor=1999$). We extend this range to 0.4999 . Therefore values of k_factor we chose to evaluate the k_factor are $20, 100, 200, 1000, 2000, 10000$.

2.2.3 Quantitative image evaluation—For each projection group, we used the original 4D-CT images as the reference image (or “ground-truth”) to evaluate the reconstructed images. We calculated different similarity metrics, including the relative error (RE) [49], the root-mean-square error (RMSE) [50], the normalized cross-correlation (NCC) [51], and the universal quality index (UQI) [52] to quantify the similarity between the reconstructed images and the reference images.

$$RE = \sqrt{\frac{\sum_N (A - B)^2}{\sum_N A^2}} \quad (11)$$

$$\text{RMSE} = \sqrt{\frac{\sum_N (A - B)^2}{N}} \quad (12)$$

$$\text{NCC} = \left\langle \frac{A}{\|A\|}, \frac{B}{\|B\|} \right\rangle \quad (13)$$

$$\text{UQI} = \frac{\sigma_{AB}}{\sigma_A \sigma_B} \cdot \frac{2\bar{a}\bar{b}}{(\bar{a})^2 + (\bar{b})^2} \cdot \frac{2\sigma_A \sigma_B}{\sigma_A^2 + \sigma_B^2} \quad (14)$$

A denotes the reference image, and B denotes the reconstructed image. N denotes the total voxel numbers of A or B . $\bar{a}$ and $\bar{b}$ denote the averages of A and B , respectively. σ_A is the standard derivation of A , and σ_B is the standard derivation of B . σ_{AB} calculates the covariance between A and B .

We made quantitative comparisons between images reconstructed by SMEIR-Bio using different projection numbers to evaluate the method's performance under different sampling sparseness. We also performed quantitative comparisons between 4D-CBCT images reconstructed by ART-TV, SMEIR and SMEIR-Bio under the same sampling sparseness. We also used one method proposed in a previous work [53]. This method follows the work frame of SMEIR and uses mesh-based representation (in contrast to voxel-based representation) to update the DVFs without considering the elastic properties of tissue, which is referred to as the “SMesh” method in the following. In addition to image reconstruction accuracy, we also measured lung motion model accuracy for each patient by comparing manually-tracked lung landmark motion with solved DVFs from different reconstruction methods. We tracked the lung landmarks displacement between the end-of-inspiration and end-of-expiration phases for evaluation, defining the displacement error $\vec{D}_{\text{error}}$ as the difference vector between the manually-tracked landmark displacement and the corresponding displacement extracted from solved DVFs. We calculated and compared the averages and standard derivations of D_{error} under each projection group.

$$\vec{D}_{\text{error}} = \vec{L}_{\text{manually}} - \vec{L}_{\text{DVF}} \quad (14)$$

$$D_{\text{error}} = \|\vec{D}_{\text{error}}\| \quad (15)$$

$\vec{L}_{\text{manually}}$ denotes the manually-tracked displacement vector composed of l_{manually}^x , l_{manually}^y , and l_{manually}^z , which denote motion along x (left-right), y (anterior-posterior), and z

(superior-inferior) spatial directions, respectively. The $\vec{L}_{DVF}$ denotes the displacement vector extracted from the solved DVFs, composed of l_{DVF}^x , l_{DVF}^y , and l_{DVF}^z . D_{error} denotes the norm-2 of the difference vector between $\vec{L}_{manually}$ and $\vec{L}_{DVF}$ or the length of the displacement error.

3. RESULTS

3.1 k_factor optimization

We evaluated the influence of different k_factor values by calculating the average $D_{error}^{SMEIR-Bio}$ of all landmarks. The corresponding results are shown in Fig. 2 and Table 2. For patient 3, patient 7, and patient 11, the length of displacement errors (D_{error}) is the smallest when the k_factor is equal to 1000 (Fig. 2). For the others, the D_{error} gradually decreases with increasing k_factor values. Overall, a k_factor of 1000 generates the highest DVF accuracy in the parameterized study (Table 2). Thus, we used this value in the following evaluations.

3.2 Reconstruction image quality

SMEIR-Bio method is evaluated using groups of different projection number. The difference between “ground-truth” and reconstructed images are made and shown in Figure 3. The difference is small, even when using 10 projections per phase for reconstruction. SMEIR-Bio method can achieve high quality image reconstruction even with small projection number. Using more projections helps to reduce the mismatches of the lung’s fine structures.

We calculated the relative error between the “ground-truth” and reconstructed images of each patient with different methods. The means and standard derivations of relative error of all patients for different projections are shown in Figure 4, for both SMEIR and SMEIR-Bio reconstructions. The relative error decreases with increasing projection number. Compared with SMEIR, SMEIR-Bio enables higher reconstruction accuracy with smaller relative errors.

To evaluate the performance of SMEIR-Bio in lung regions with small fine details, we performed quantitative comparisons on 10 intra-lung regions with fine pulmonary structures for all patients. 6 of the 10 selected regions of interest (ROIs) of patient 1 and patient 10 are shown in Figure 5. The SMEIR-Bio reconstructs fine lung details that better match the “ground-truth” than the other two reconstruction techniques, in terms of both structure shape and intensity. Quantitative results of the comparison between ROIs demonstrate the superiority of SMEIR-Bio in reconstructing areas with small, fine details (Figure 6).

The DVF accuracy, evaluated through manually-tracked lung landmarks, is shown in Fig. 7. The landmarks displacement error calculated from different methods, SMEIR-Bio and SMEIR, using 30 projections per phase for reconstruction, along each of the Cartesian directions, x, y and z, is shown along with the D_{error} . In x and y direction, 9 out of 11 patients’ displacement error for SMEIR-Bio are smaller than that for SMEIR. In z direction, all patients’ displacement errors calculated from SMEIR-Bio are smaller than SMEIR. As lung motion occurs predominantly in the z (superior-inferior) direction, we specifically extracted DVFs in the z direction and calculated the corresponding landmarks displacement

error between manually-tracked landmark motion and landmark motion extracted from DVFs. The average displacement difference along the z direction of all 11 patients is 2.49 mm for SMEIR-Bio and 4.03 mm for SMEIR. The average D_{error} of all 11 patients is 3.56 mm for SMEIR-Bio and 4.97 mm for SMEIR. We observed a statistically significant difference ($p = 0.0013$, by Wilcoxon signed-rank test) between $D_{error}^{SMEIR-Bio}$ and D_{error}^{SMEIR} .

The comparison between SMEIR and SMEIR-Bio reconstruction results based on real 4D CBCT patient data are showed below in Figure 8 and Table 3. In the Figure 8, the truncation artifacts are caused by the limited field of view during projection acquisition.

As shown in Figure 8 and Table 3, SMEIR-Bio can reconstruct images, especially the intra-lung details with higher accuracy. Using real clinical projections with scatter, noise and beam hardening, SMEIR-Bio outperforms SMEIR, and reconstructs images with fine lung details matched to the “gold-standard” reference image reconstructed from dense projections.

The effects brought by segmentation are evaluated. Visual and quantitative results for two patients are shown in Figure 9 and Table 4.

As demonstrated in the Figure 9, segmentation masks generated using different methods have various boundaries especially around heart. However, when applied to the SMEIR-Bio, all of them can achieve high accuracy reconstruction compared with the ground-truth image. The reconstructed images share visual similarity. The effects of segmentation are quantified in Table 4. Lung regions are extracted to calculate RMSE, RE and NCC. The results show that reconstructed images are of similar accuracy when different segmentation methods are applied.

4. DISCUSSION AND CONCLUSION

We developed the SMEIR-Bio technique based on the SMEIR algorithm for 4D-CBCT reconstruction but added biomechanical modeling to the workflow to improve DVF and image reconstruction accuracy in low-contrast regions or regions with small fine details. Lung surface DVFs solved by 2D–3D deformation, whose accuracy benefits from the high-contrast lung boundary, served as the boundary condition to drive finite element analysis-based biomechanical modeling to fine-tune the intra-lung DVFs [54]. Based on our evaluation using 11 lung cancer patient cases, the proposed SMEIR-Bio algorithm enhances the reconstructed 4D-CBCT quality, as well as the accuracy of inter-phase DVFs. The accurate 4D-CBCT and DVFs have the potential to be applied to patient setup, tumor tracking, dose accumulation, and adaptive radiation therapy [55, 56].

Our work viewed the intra-lung structures as homogeneous in material. In reality, however, there are various heterogeneous structures within the lung, including bronchi and lung vessels. In addition, for patients who have large areas of necrosis, inflammation or pneumonitis in lung, the lung tissue elasticity may also vary from region to region. Correspondingly, the solved intra-lung DVF under the homogeneity assumption can be error-prone in these regions. Therefore, future research should consider different elastic properties and model the interactions between different structures inside the lung to achieve

a more biomechanically realistic deformation. Multi-organ deformation analysis based on the biomechanical modeling method can be applied to SMEIR-Bio to simulate the lungs' motion in light of their interactions with different organs [47]. This analysis views the thoracoabdominal region as a whole and simulates the motion of organs that do not have a clear boundary using adjacent organs' motion. Furthermore, the air low mechanics inside the lung could also be modeled to improve the accuracy of biomechanical modeling [57].

The proposed SMEIR-Bio method also requires more computation time than SMEIR because of the additional biomechanical modeling component. Currently, we only use the CPU for image reconstruction. Within each iteration, the motion-compensated reconstruction takes about 25 minutes, the 2D–3D registration takes about 20 minutes, and the biomechanical modeling takes about 20 minutes. For all 11 patients, 7–10 iterations were needed for SMEIR-Bio to converge. GPU programming as well as multi-threading in the CPU can help accelerate the image reconstruction process.

In summary, the developed SMEIR-Bio method enhances DVF accuracy of inside lung region with fine structures. It could potentially be used in other regions with periodic motion to image volumetric anatomy of different phases, such as livers.

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Figure 1.
Workflow of SMEIR-Bio.

Figure 2.

The average of all landmarks of $D_{error}^{SMEIR-Bio}$ for each patient using different k_factor values.

Figure 3.

Comparison between the reference phase (phase 0) images reconstructed by SMEIR-Bio using different numbers of projections. The left four columns show the reconstruction results using 10, 20, 30, and 40 projections, respectively. The rightmost column shows the same slice of the original CT image for comparison. The first row shows the reconstructed images with different projection number groups for patient 1, and the second row shows the difference image between the original CT image and the reconstructed images. The third row shows the reconstructed images with different projection number groups for patient 6, and the fourth row shows the difference image between the original CT image and the reconstructed images. The display window of the reconstructed images is $[-1000, 635]$ HU, and the display window of the error images is $[-1000$ to $-455]$ HU.

Figure 4. Average values with standard derivations for the relative error metric between reconstructed images and original “ground-truth” CT images (Phase 0) for all patients.

(A)

Figure 5.

Extracted and zoomed details for 6 of the 10 regions of interest (ROIs) in the reference phase (phase 0) image of (A) patient 1, (B) patient 10. The extracted ROIs are highlighted with red squares in each left-column slice. The four columns on the right display the same ROIs extracted from images reconstructed by ART-TV, SMesh, SMEIR, and SMEIR-Bio, reconstructed with 30 projections per phase, and from the original “ground-truth” CT image. The display window for all images is $[-1000, 635]$ HU.

(A)

(B)

Figure 6. Quantitative comparison between ART-TV, SMesh, SMEIR and SMEIR-Bio with different projection number per phase. (A)RMSE; (B)UQI; (C) NCC.

Figure 7.

Average length of displacement error for all patients (1–11) along each of the three spatial directions (left-right (X direction), anterior-posterior (Y direction), and superior-inferior (Z direction)) and D_{error} . Errors along each Cartesian direction and 3D vector errors are shown. For each patient, the left bar denotes the average displacement error of SMEIR reconstructions. The right bar denotes the corresponding error of SMEIR-Bio reconstructions. All reconstructions used 30 projections per phase.

Figure 8.

Comparison of patient 4D CBCT image at reference phase 0 reconstructed by SMEIR and SMEIR-Bio with the “gold-standard” reference image. The first row shows images reconstructed by SMEIR and SMEIR-Bio, as well as the reference image. The second row shows 2 zoomed-in intra-lung ROIs. Note that the truncation artifacts are caused by the limited field of view during projection acquisition.

Figure 9.

SMEIR-Bio reconstructed images at reference phase 0 with different segmentation methods (“snake”, thresholding, edge-attraction, clustering and classification) for (A) patient 1 and (B) patient 2. For both (A) and (B), the first row shows lung segmentation using different methods; the second row shows images reconstructed by SMEIR-Bio using different segmentations, as well as the reference CT image; the third and fourth rows show intra-lung details extracted from second row. The display window for the second row is $[-1000, 635]$ HU and is the same for zoomed-in region 1 and region 2.

Table 1

Previous studies on lung modeling. The Poisson's ratio used in each study and the corresponding k_factor for the Mooney-Rivlin model are shown.

Previous Studies	Poisson's Ratio	k_factor
Lai-Fook S J <i>et al.</i> (ref. [46])	0.43	27
SH Sundaram, CC Feng (ref. [19])	0.45	40
Brock KK <i>et al.</i> (ref. [47])	0.45	40
A. Al-Mayah <i>et al.</i> (ref. [23])	0.4, 0.45, and 0.499	19, 40 and 2000
J Eom <i>et al.</i> (ref. [25])	0.4	19

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Table 2
The average of all landmarks of $D_{\text{error}}^{\text{SMEIR-Bio}}$ for all 11 patients using different k_factor values.

k_factor	20	100	200	1000	2000	10000
MEAN D_{error} (mm)	4.151 ± 0.659	3.719 ± 0.656	3.592 ± 0.656	3.460 ± 0.645	3.465 ± 0.646	3.539 ± 0.654

Table 3

Quantitative evaluation of patient 4D CBCT images at reference phase 0 reconstructed by SMEIR and SMEIR-Bio. The images reconstructed from fully-sampled dense projections are used as the reference for evaluation.

	RMSE	RE	NCC	UQI
SMEIR	0.0033	15.22%	0.9383	0.9038
SMEIR-Bio	0.0031	14.53%	0.9435	0.9377

Quantitative accuracy of the lung regions reconstructed by SMEIR-Bio with different segmentation methods at the reference phase 0 using 30 projections from patient 1 and patient 2. The original 4D-CT image is used as the reference for evaluation.

Table 4

	Patient 1				Patient 2			
	RMSE	RE	NCC	UQI	RMSE	RE	NCC	UQI
Thresholding	0.0033	14.38%	0.9778	0.8972	0.0035	13.52%	0.9724	0.8564
Edge-Attraction	0.0033	14.47%	0.9782	0.9011	0.0035	14.28%	0.9728	0.8723
Clustering	0.0032	13.69%	0.9794	0.8989	0.0036	14.54%	0.9714	0.8647
Classification	0.0033	14.05%	0.9790	0.9004	0.0035	14.22%	0.9729	0.8596
SNAKE	0.0032	14.29%	0.9780	0.8996	0.0036	14.43%	0.9725	0.8820