Towards Respiration Management in Radiation Treatment of Lung Tumors: Transferring Regions of Interest from Planning CT to Kilovoltage X-ray Images

Esra Ataer-Cansizoglu[¶], Erhan Bas[¶], M. Ali Yousuf[§], Sheng You[¶], Warren D. D'Souza[§], Deniz Erdogmus[¶]

Abstract— **Tracking of lung tumors is imperative for improved radiotherapy treatment. However, the motion of the thoracic organs makes it a complicated task. 4D CT images acquired prior to treatment provide valuable information regarding the motion of organs and tumor, since it is manually annotated. In order to track tumors using treatment-day X-ray images (kV images), we need to find the correspondence with CT images so that projection of tumor region of interest will provide a good estimate about the position of the tumor on the X-ray image. In this study, we propose a method to estimate the alignment and respiration phase corresponding to X-ray images using 4D CT data. Our approach generates Digitally Reconstructed Radiographs (DRRs) using bilateral filter smoothing and computes rigid registration with kV images since the position and orientation of patient might differ between CT and treatment-day image acquisition processes. Instead of using landmark points, our registration method makes use of Kernel Density Estimation over the edges that are not affected much by respiration. To estimate the phase of X-ray, we apply template matching techniques between the lung regions of X-ray and registered DRRs. Our approach gives accurate results for rigid registration and provides a starting point to track tumors using the X-ray images during the treatment.**

I. INTRODUCTION

Radiotherapy is an effective treatment technique for lung cancer. However, the movement of lung tumors during normal respiration makes it difficult to accurately irradiate the tumor. Precise lung tumor localization is vital to efficiently treating the tumor and avoiding unnecessary radiation exposure of normal tissues. Estimating the motion model of the tumor may lead to improved treatment planning and dose calculation throughout the therapy. 4D Computed Tomography (CT) images taken prior to treatment (to develop the patient's treatment plan) provide valuable information about the movement of the thoracic organs and the tumor. For each radiotherapy treatment session, a set of kilovoltage X-ray images (kV images) are acquired to aid in the alignment of the treatment target relative to the radiation beam. However, the position and orientation of the patient might differ between CT and treatment-day image acquisition processes. Further, kV images are typically acquired at an arbitrary phase of the respiration cycle. The problem is further compounded by the fact that soft-tissue targets (e.g., tumor) are not readily identified on kV images, thus making it difficult for the operator to determine the optimal patient alignment. In order to accurately deliver the planned radiation treatment, a spatial match between the alignment of soft-tissue targets between the CT and kV image must be achieved. In this study, we propose a method to estimate the respiration phase of a given treatment X-ray image, which yields an estimate of tumor position by taking the projection of the corresponding 4D CT phase.

Respiratory gating technique is sometimes used to overcome the affect of tumor motion. Cui et al. [2] proposed a correlation based method for gating in lung cancer radiotherapy. They compare various template matching schemes, considering single and multiple templates and template clustering. In another study [3] template matching over a search region was used to track the tumor over X-ray images. They define the position of the tumor as a weighted sum of tumor locations in the reference templates, where weights are determined based on correlation scores. Rottman et al. [6] presented a multi-region tracking algorithm to track lung tumors over CT projections and in-treatment portal image movies. They used correlation as a similarity measure to find the most likely position of the tumor among the candidate landmark points which are generated by choosing regions of maximal texture.

Zeng et al. [8] proposed a non-rigid motion estimation method to register a conventional breath hold X-ray with the projection views acquired from a Cone Beam CT. They deform the projection of the reference frame to register it with each frame of CBCT sequence, where the reference is a conventional CT taken during the breath hold condition. Chen et al. [1] presented a 3D-2D registration method by searching over possible rotation and translations and using correlation between X-ray and DRR strips as a similarity measure. The method involves constructing the DRR partially to create a Digitally Reconstructed Radiograph (DRR) strip corresponding to the boundaries of the skull.

The contributions of this paper are: *(i)* a bilateral filtering based interpolation technique for generating DRRs that can filter out undesired tissue intensities and maintain edges of internal lung structures, *(ii)* a multi-DRR to X-ray edge-distribution registration algorithm based on kernel density estimation, and *(iii)* a region-of-interest-based correlation

This work was partially supported by NSF grants ECCS0929576 and ECCS0934506.

[¶]Department of Electrical and Computer Engineering, Northeastern University, Boston, MA 02115, USA ataer@ece.neu.edu, bas@ece.neu.edu, you.sh@neu.edu, erdogmus@ece.neu.edu

[§]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD 21201, USA myousuf@umm.edu, wdsou001@umaryland.edu

coefficient score technique that yields high confidence respiration phase estimates for X-ray images given 4D CT projections in the same plane. The goal of this study is to investigate the feasibility of automatic the transfer of regions-of-interest from 4D CT images to treatment-day kV images to identify soft-tissue target alignment accurately prior radiation delivery.

II. METHOD

4D CT data contains the 3D CT images of a patient for each phase of the respiration cycle. The physicians label this data to make an initial treatment plan, hence we have information regarding the position and structure of the organs and tumors for the CT images. Once, we affiliate the X-ray image with one of the CT images, we are able to make an estimation about the position of the tumor by taking the projection of the Region of Interest (ROI) of the tumor. In order to find the relation between 4D CT data and X-ray image, we first generate DRRs in the X-ray plane by calculating the projection of CTs in the beam's eye view. Next, we achieve rigid registration between DRRs and X-ray, since patient position and orientation may be different in CT and X-ray acquisition sessions. Lastly, we relate the X-ray with one of the CTs and answer the question *'which respiration phase of the 4D CT, the X-ray image corresponds to'*. This enables us to determine the most likely position of the tumor on the X-ray by getting the projection of the tumor region from the corresponding CT phase.

A. Generation of DRRs

Generation of DRRs involves the simulation of the X-ray image given phase 3D CT data. In order to construct the DRR, rays are passed through the CT originating from the position of the X-ray source. Intensity integration over the simulated rays will give us the intensity value at the position which the ray falls on the simulated receiver. Hence, interpolation techniques are necessary to assign CT intensity values to the points on the simulated rays. One basic method is to use zero-order hold. Basically, this technique assigns the intensity value of the nearest voxel to point. Assume $\mathbf{q}$ is an arbitrary point on the ray and $\mathbf{v}$) is the closest voxel to point $\mathbf{q}$. Then, the intensity value of the point $\mathbf{q}$ is assigned as $I(\mathbf{q}) = I(\mathbf{v})$ where $I(\mathbf{x})$ represents the intensity value of point $\mathbf{x}$. Note that Euclidean distance is used and the position of the voxel is assumed to be the center.

A better technique for interpolation involves bilateral filtering [7]. This method assigns the weighted sum of intensity values of the nearest K voxels to the point. Given $d(\mathbf{p}, \mathbf{q})$ representing the distance between points $\mathbf{p}$ and $\mathbf{q}$, and $N_{\mathbf{q}}$ as the set of nearest K voxels to the point $\mathbf{q}$, the intensity value at point $\mathbf{q}$ is

$$I(\mathbf{q}) = \sum_{\mathbf{p} \in N_{\mathbf{q}}} w_{\mathbf{p}} I(\mathbf{p}) \tag{1}$$

where

$$\tilde{w_{\mathbf{p}}} = exp\frac{-1}{2}(\frac{d(\mathbf{p}, \mathbf{q})}{\sigma})^2 \tag{2}$$

$$w_{\mathbf{p}} = \frac{\tilde{w_{\mathbf{p}}}}{\sum_{\mathbf{r} \in N_q} \tilde{w_{\mathbf{r}}}} \tag{3}$$

In comparison to the zero-order hold method, this technique might give smoother DRRs, since it weights the intensity values of the neighbors with an exponential function [1]. We can extend the weight term by taking the diversity among intensity values of the neighboring voxels into consideration. In order to increase the impact of intensity values that are closer to the color of the nearest voxel, we extend the weight term in the following way

$$w_{\mathbf{p}} \propto w_{\mathbf{p}}^{(p)} w_{\mathbf{p}}^{(c)} \tag{4}$$

$$w_{\mathbf{p}}^{(p)} = exp(-d^2(\mathbf{p}, \mathbf{q})/(2\sigma_{\mathbf{p}}^2)) \tag{5}$$

$$w_{\mathbf{p}}^{(c)} = exp(-d^2(I(\mathbf{p}), I(\mathbf{v}))/(2\sigma_c^2)) \tag{6}$$

where the final weight $w_{\mathbf{p}}$ is normalized to add to unity over the contributing neighbor voxels, and $d(\mathbf{p}, \mathbf{q})$ and $d(I(\mathbf{p}), I(\mathbf{q}))$ are the distance between coordinates and intensities respectively. The latter version of the weight improves the effect of nearest intensities that resemble to the nearest voxel of the current point to be interpolated, which is expected to be closer to the true color of the point. This allows the DRRs to be generated using an edge preserving fashion.

B. Rigid Registration

After the construction of DRRs we have the projection of CTs corresponding to phases of a respiration cycle. Assuming that the patient does not move during CT acquisition process [2], we are interested in finding the rigid registration between the DRRs and the X-ray image. Hence, we need landmark points that are not affected by respiration. However, accurate selection of single points (such as corners or intersections of edges) is hard for an operator/technician due to the high levels of noise on the images (especially in the kV X-ray images). Instead, we prefer to utilizing highlighted edges that are stationary in the DRRs across respiratory phases, and by utilizing kernel density estimation over the edge pixels we are able to find the rigid transformation between the stationary anatomy visible in the DRRs and the X-ray images.

Consider a general weighted variable-width kernel density estimate (KDE) obtained from samples $\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_N \in \mathbb{R}^d$. KDE is given as

$$\zeta(\mathbf{x}) = \sum_{i=1}^{N} w_i G_{\mathbf{\Sigma}_i}(\mathbf{x} - \mathbf{x}_i) \tag{7}$$

[1]Note that this process, when weights of neighboring voxels are selected by a decaying kernel by distance, essentially corresponds to kernel or spline interpolation.

[2]We have verified visually that across DRRs for different phases of respiration, the bony anatomy that does not move with respiration remain stationary and well registered to each other. Consequently, registration across DRRs for different phases is not required in our particular datasets - however, the procedure described in this section can be utilized to achieve such a registration if needed in other situations.

where w_i is the weight and $\mathbf{\Sigma}_i$ is the variable kernel covariance of the Gaussian kernel $G_{\mathbf{\Sigma}_i}(\mathbf{x}_i) = C_{\mathbf{\Sigma}_i} e^{-\frac{1}{2}\mathbf{x}_i^T \mathbf{\Sigma}_i^{-1} \mathbf{x}_i}$ for the i^{th} data sample $\mathbf{x}_i$. Consider a function $\mathbf{f} : \mathbb{R}^d \rightarrow \mathbb{R}^d$ between the selected edges of DRRs and X-ray. A rigid transformation can be written as $\mathbf{y} = \mathbf{f}(\mathbf{x}) = \mathbf{R}(\mathbf{x} + \mathbf{t})$ where $\mathbf{R}$ is a d-by-d rotation matrix and $\mathbf{t} \in \mathbb{R}^d$ is the translation vector. The parameters of the rigid registration ($\mathbf{R}$, $\mathbf{t}$) are selected such that the inner product between the density functions $\zeta_1(\mathbf{x})$ and $\zeta_2(\mathbf{f}(\mathbf{x}))$ is maximized, where ζ_1 and ζ_2 are the KDE estimates of a single phase DRR and X-ray respectively. Inner product between two scalar valued functions can be written as

$$\begin{aligned} I(\zeta_1(\mathbf{x}), \zeta_2(\mathbf{f}(\mathbf{x}))) &= \int_{-\infty}^{\infty} \zeta_1(\mathbf{x}) \zeta_2(\mathbf{f}(\mathbf{x})) d\mathbf{x} \\ &= \int_{-\infty}^{\infty} \sum_{i=1}^{N_1} w_i G_{\mathbf{\Sigma}_i}(\mathbf{x} - \mathbf{p}_i) \sum_{j=1}^{N_2} v_j G_{\mathbf{\Gamma}_j}(\mathbf{x} - (\mathbf{R}(\mathbf{q}_j - t)) d\mathbf{x} \\ &= \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} w_i v_j \int_{-\infty}^{\infty} G_{\mathbf{\Sigma}_i}(\mathbf{x} - \mathbf{p}_i) G_{\mathbf{R}^T \mathbf{\Gamma}_j \mathbf{R}}(\mathbf{x} - (\mathbf{q}_j - t)) d\mathbf{x} \\ &= \sum_{i=1}^{N_1} \sum_{j=1}^{N_2} w_i v_j G_{\mathbf{\Sigma}_i + \mathbf{R}^T \mathbf{\Gamma}_j \mathbf{R}}(\mathbf{p}_i - \mathbf{q}_j + \mathbf{t}) \end{aligned} \tag{8}$$

Here $\mathbf{p}_i$ and $\mathbf{q}_j$ represent edge sample coordinates selected from various phases of the DRRs and the X-ray. w_i and v_j are the weights [3], $\mathbf{\Sigma}_i$ and Γ_j are the variable size kernel covariances of the the samples $\mathbf{p}_i$ and $\mathbf{q}_i$ respectively. In order to find the rigid transformation parameters, we employed a direct search method [5] that is available in Matlab. Specifically we solve $\underset{\mathbf{R},\mathbf{t}}{\operatorname{argmax}} \sum_l I(\zeta_{DRR_l}, \zeta_{X-ray})$.

C. Phase Estimation

Once we obtain the rigid registration between the X-ray and the DRRs, with the observation that lung regions change more during respiration, the similarity between lung regions of DRRs and X-ray is used to estimate the respiratory phase that corresponds to the particular X-ray image. We compute the correlation coefficient (denoted by ρ) between each DRR and X-ray over lung regions that are automatically found by the projection of lung boundaries given for the CT.

Assume I_i is the selected image patch on the i^{th} DRR and T is the reference patch corresponding to the X-ray. Correlation coefficient between I_i and T, $\rho(I_i, T)$, is computed as

$$\rho(I_i, T) = \frac{E[I_i \cdot T]}{\sqrt{E[I_i \cdot I_i] E[T \cdot T]}} \tag{9}$$

where N is the number of pixels in each patch and $E[I \cdot J]$ represents the correlation between image I and J obtained by pixel-wise inner product.

$$E[I \cdot J] = \sum_{\mathbf{p}} I(\mathbf{p}) J(\mathbf{p}) - \frac{1}{N} \sum_{\mathbf{p}} I(\mathbf{p}) \sum_{\mathbf{p}} J(\mathbf{p}) \tag{10}$$

The DRR corresponding to the actual phase of the X-ray is expected to show the maximum correlation coefficient among all available DRRs. We employ the Jackknife leave-one-out mean and variance estimates [4] to obtain the expected lung-region correlation coefficient between each DRR and X-ray image and its variance in order to see whether the difference between correlation values are statistically significant.

Suppose ρ_i^p is the correlation coefficient of the X-ray and the p^{th} DRR computed by leaving the i^{th} pixel out over lung region and N is the number of pixels inside the region. Sample average of the correlation coefficient is

$$\hat{\rho}^p = \frac{1}{N} \sum_{i=1}^{N} \rho_i^p \tag{11}$$

Jackknife estimate of the variance is,

$$var(\rho^p) = \frac{N-1}{N} \sum_{i=1}^{N} (\rho_i^p - \hat{\rho}^p)^2 \tag{12}$$

and the unbiased Jackknife estimate of the correlation coefficient is,

$$\tilde{\rho}^p = N\rho^p - (N-1)\hat{\rho}^p \tag{13}$$

where ρ^p is the correlation coefficient computed using all pixels.

III. EXPERIMENTS AND RESULTS

The experiments are carried out on 4D CT and X-ray images of 2 patients in coronal view. For the construction of DRRs, bilateral interpolation with spatial and intensity values is used, since it gives smoother DRRs in comparison to the zero-order hold method, while preserving edges. Bilateral interpolation method might be computationally expensive, as number of neighboring voxels, K, increases. Hence, after observing some results for different values of K, we preferred to set number of neighboring voxels to 10. In order to enhance the contrast of images, we applied adaptive histogram equalization as a post-processing step. Figure 1 displays the generated DRRs for one of the CTs of the patients along with the X-ray images.

At the rigid registration process, an operator manually selected edges from bony structures that are not affected by breathing and therefore remain stationary across DRRs. The rigid registration solution is computed using the edge density correlation method described above and using edges from all DRRs simultaneously to reduce sensitivity to manual edge tracing errors. Figure 2 shows the selected edges on the X-ray image and the correlation coefficient between X-ray and one of the registered DRRs. Upon determining the optimal rigid registration solution between the DRRs and the X-ray using the registering technique presented above, each pixel's local correlation coefficient in a 15x15 region surrounding it is computed between the DRRs and the X-ray. We observe high correlations on the edges selected for rigid registration, which shows the accuracy of the registration algorithm. Note that manual selection of landmark edges is not tedious and this process very much fits within the clinical work flow.

We compute the Jackknife estimate of correlation coefficient between the X-ray and DRRs over lung regions, which move fast during breathing. Figure 3 shows the projection of the lung region in the CT onto the X-ray image. The plot

[3] Selected to be equal here, but could also be adopted from the image using an edge level estimator such as the magnitude of the intensity gradient at this position.

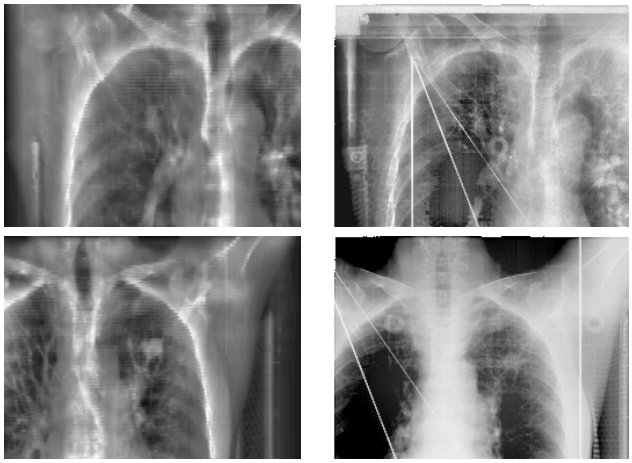

Fig. 1. Generated DRRs for one of the CTs of each patient (top left and bottom left), X-ray images (top right and bottom right)

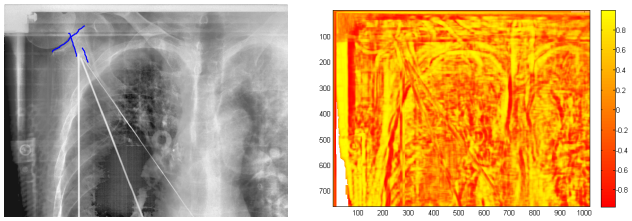

Fig. 2. Selected edges for registration on X-ray(left), correlation values between X-ray and one of the registered DRRs based on a 15x15 sliding window around each pixel(right)

of Jackknife estimates of correlation coefficient for DRRs can be seen in Figure 4. As seen in the figure, standard deviation values are very small compared to the difference between unbiased correlation coefficient estimates. Thus, the peak at phase 4 provides a statistically reliable information to estimate the phase of the X-ray. Based on the plots, one can conclude that X-rays for both patients correspond to phases 3, 4 and 5 of the respective treatment planning 4D CT images.

IV. CONCLUSION

We have proposed a method to transfer regions of interest from 4D CT images to treatment-day kV images in order align soft tissues prior to radiation delivery. Our approach estimated the respiration phase corresponding to a given coronal plane X-ray taken during treatment preparation. Given 4D CT data that is used for initial treatment planning, the method generates DRRs using bilateral interpolation

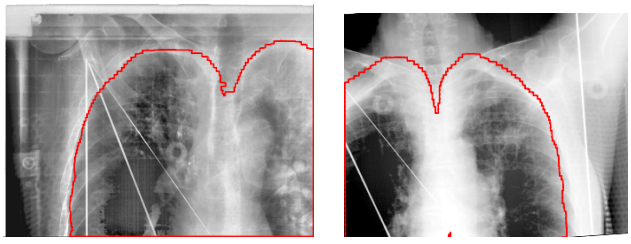

Fig. 3. Projected lung regions for patient 1 (left) and patient 2 (right)

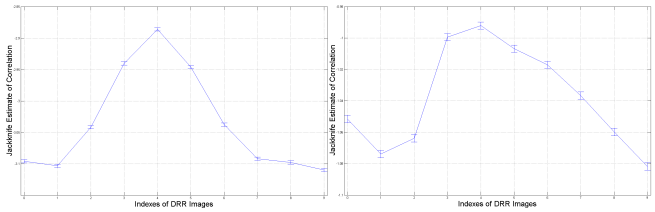

Fig. 4. Jackknife estimate of correlation between X-ray and each DRR over the lung regions for patient 1 (left) and patient 2 (right). Bars represent 3 times standard deviation for each correlation coefficient. Note that phases are indexed from 0 to 9 and phase 1 corresponds to end exhale CT for both patients.

and computes the rigid registration between these for each respiratory phase and the X-ray image by using kernel density estimation over manually selected landmarks which lay over the edges not affected from breathing. Our registration method gives accurate results in preliminary studies shown here. Correlation coefficient between the lung regions of X-ray and registered DRRs gives important information regarding respiration phase.

In the future, we aim to use the estimated phase to initialize the tracking of tumors in the X-ray video that is taken on treatment day. Tracking of tumor will provide crucial information regarding its trajectory on the particular treatment day. This will enable the physicians to observe/estimate the motion of the tumor in real time and irradiate it efficiently. Since our dataset consists of images from the coronal plane, a 2D registration method was sufficient. We will extend our registration method to find the rotation and translation of patient in 3D so that phase estimation technique can benefit from X-ray images in the sagittal plane as well. This will also allow 3D tumor trajectory modeling.

REFERENCES

[1] Xin Chen, Martin R. Varley, Lik-Kwan Shark, Glyn S. Shentall, and Mike C. Kirby, *Automatic 3d-2d image registration using partial digitally reconstructed radiographs along projected anatomic contours*, MEDIVIS '07: Proceedings of the International Conference on Medical Information Visualisation - BioMedical Visualisation, 2007, pp. 3–8.

[2] Ying Cui, Jennifer G Dy, Greg C. Sharp, Brian Alexander, and Steve B. Jiang, *Robust fluoroscopic respiratory gating for lung cancer radiotherapy without implanted fiducial markers*, Phys. Med. Biol. **52** (2007), 741–755.

[3] Ying Cui, Jennifer G Dy, Gregory C Sharp, Brian Alexander, and Steve B Jiang, *Multiple template-based fluoroscopic tracking of lung tumor mass without implanted fiducial markers*, Phys. Med. Biol. **52** (2007), 6229–6242.

[4] R. O. Duda, P. E. Hart, and D. G. Stork, *Pattern classification*, Wiley-Interscience Publication, 2000.

[5] J. A. Nelder and R. Mead, *A Simplex Method for Function Minimization*, The Computer Journal **7** (1965), no. 4, 308–313.

[6] Joerg Rottmann, Ross Berbeco, Michalis Aristophanous, and Sang-June Park, *Multi-region tracking for lung tumor motion assessment*, International Conference on Machine Learning and Applications (2009).

[7] C. Tomasi and R. Manduchi, *Bilateral filtering for gray and color images*, ICCV '98: Proceedings of the Sixth International Conference on Computer Vision, 1998, p. 839.

[8] Rongping Zeng, Jeffrey A. Fessler, and James Balter, *Respiratory motion estimation from slowly rotating x-ray projections*, Symposium A Quarterly Journal In Modern Foreign Literatures (2004), 480–483.