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A GRADIENT FEATURE WEIGHTED *MINIMAX* ALGORITHM FOR REGISTRATION OF MULTIPLE PORTAL IMAGES TO 3DCT VOLUMES IN PROSTATE RADIOTHERAPY

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Abstract

Purpose—To develop an accurate, fast, and robust algorithm for registering portal and computed tomographic (CT) images for radiotherapy using a combination of sparse and dense field data that complement each other.

Methods and Materials—Gradient Feature Weighted Minimax (*GFW Minimax*) method was developed to register multiple portal images to three-dimensional CT images. Its performance was compared with that of three others: *Minimax*, Mutual Information, and Gilhuijs' method. Phantom and prostate cancer patient images were used. Effects of registration errors on tumor control probability (TCP) and normal tissue complication probability (NTCP) were investigated as a relative measure.

Results—Registration of four portals to CTs resulted in 30% lower error when compared with registration with two portals. Computation time increased by nearly 50%. *GFW Minimax* performed the best, followed by Gilhuijs' method, the *Minimax* method, and Mutual Information.

Conclusions—Using four portals instead of two lowered the registration error. Reduced fields of view images with full feature sets gave similar results in shorter times as full fields of view images. In clinical situations where soft tissue targets are of importance, *GFW Minimax* algorithm was significantly more accurate and robust. With registration errors lower than 1 mm, margins may be scaled down to 4 mm without adversely affecting TCP and NTCP.

Keywords

Multimodality image registration; Prostate radiotherapy; Patient positioning; Tumor control probability; NTCP

INTRODUCTION

The aim of three-dimensional conformal radiotherapy (3DCRT) is to deliver a precise dose of radiation to the tumor, while sparing adjacent normal tissues. To achieve maximum benefit, radiation beams from multiple directions are shaped to conform to the projected outline of the

tumor. Recent developments such as intensity-modulated radiotherapy (IMRT) modulate the intensities within each beam using volumetric imaging data (1). Treatment planning is usually done using three-dimensional computed tomographic (3DCT) images and computerized dose calculations to realize an intensity pattern that best corresponds to the tumor shape. As the dose is delivered in multiple fractions, in both 3DCRT and IMRT, correct patient positioning is crucial to realizing the maximum potential of the therapy. Traditionally, patient positioning parameters are estimated by a visual comparison of portal and simulator images. Investigators have reported that in 22% of the cases, errors between 5 and 10 mm are common (2). Immobilization devices and surgically implanted gold fiducials have minimized errors to some extent (3), but have often proved to be inadequate because of patient discomfort, cost, and internal organ motion between and during treatment fractions (4,5). To overcome these limitations, the planning margins around the target are chosen to be large enough to include maximum excursions outside the targeted volume. This approach compromises normal tissue safety. Currently, the target volume is delineated by a clinician through the use of a 3D data set such as CT or another 3D imaging modality. A plan is then developed that takes into account microscopic tumor spread, organ motion, and patient positioning uncertainty that will deliver radiation to the tumor while causing tolerable harm to normal tissues. To confirm that the treatment is being administered as prescribed, digitally reconstructed radiographs (DRRs) from the 3DCT data set or kilovoltage radiographs (simulator films) are used as templates to guide corrections to the patient position as documented on the linear accelerator with megavoltage energy radiographs. Unless gold fiducial markers have been placed in a soft tissue target such as the prostate, skeletal bone is used as a surrogate structure for assessing positioning accuracy. All these manual matching or registration methods are laborious and time-consuming. Since the early 1990s, considerable research has been devoted to automating the process of patient positioning resulting in a multitude of methods aimed at registering 3DCT data to portal images.

The most popular registration methods may be classified as *dense field (intensity-based)* and *sparse field (feature-based)* techniques. Dense field methods are robust to noise and blur, but are computationally expensive. Lemieux utilized an automated pixel intensity correlation-based method to register 3DCT data to two portal images (6). Berger and Gerig used a least-squares template matching algorithm to register DRRs to portals (7). Hristov and Fallone proposed a correlation-based registration method to align portal and simulator images (8). Dong and Boyer registered portal images to megavolt DRRs by optimizing the cross-correlation coefficient in regions of interest (9). Weese *et al.* employed a pattern intensity-based similarity measure for voxel-based registration of 3DCT images and intratreatment X-ray fluoroscopy images (10). All these methods are quite robust but are computationally expensive.

Sparse field methods extract homologous features and use them to estimate the alignment. Some methods extract natural features such as edges, ridges, and contours in the images, whereas others locate fiducial markers that have been implanted before imaging. Fritsch *et al.* introduced a multiscale method based on *cores* that extracts salient anatomic features for registration (11). Balter *et al.* used manually digitized open curve segments for registering two-dimensional projection radiographs (12). Gilhuijs *et al.* extracted ridge-like features from portal images and matched them to projections through CT data (13). In earlier attempts, Gilhuijs and van Herk used the arithmetic mean of a neighborhood of pixels sampled from a distance transformed image as the cost function for registration (14). Leszczynski *et al.* extended this cost function to include a root mean square distance (15). In 1995, Gilhuijs described a method that extracts bony ridges from images, to automatically register 3DCT data to orthogonal portal images for patient setup verification (16). Stoeckel *et al.* introduced tensor-based scaling parameters to suppress spurious ridges in portal images before registration (17). All these algorithms act on sparser data and are computationally less expensive, but are limited by the accuracy of feature extraction.

In this article, we present the results of registering multiple ($n \geq 2$) two-dimensional portal images to 3DCT volumetric data using an iterative procedure called the *Minimax* entropy algorithm, which was initially a dense field metric. The initial algorithm registered 3DCT of a phantom to two orthogonal full field of view (FOV) portals (anterior-posterior [AP] and left-lateral [LL]) (18). The *Minimax* algorithm was extended to use a mixture of dense and sparse field information, and is termed the *Gradient Feature Weighted Minimax (GFW Minimax)* method. It has the flexibility to use up to four portal images with full and reduced fields of view (FFOV and RFOV). The RFOV portals are representative of views projected by 3DCRT or IMRT beams. The portals were acquired such that no two images represented the same views. The results of the algorithm were compared with the values estimated by two other popular algorithms: Mutual Information (MI) (19) and Gilhuijs' feature-based method (13, 14). All algorithms were tested on both phantom and patient data. We also present work done to increase the computational efficiency of the algorithm. This was done by estimating the *probability density functions (pdfs)* using a *Support Vector Machine (SVM)* based method instead of the initial *Parzen Windows (PW)* method.

As the issue of prostate positioning relative to the dose plan continues to be of interest, we investigated the effects of the errors in algorithm-derived patient setup parameters on the tumor control probability (TCP) and the normal tissue complication probability (NTCP). TCP is a measure of the effectiveness of the administered therapy in destroying the malignant cells within the target volume, and NTCP is an estimate of the risk to the neighboring normal organs. These two parameters can potentially be used to measure the success of a treatment plan (20, 21). The standard procedure is to manually contour the prostate on CT images and generate a planning target volume (PTV) by providing a margin of nearly 10 mm around it to ensure dose delivery to a clinical target volume (CTV) that encompasses the entire possible range of prostate locations. This results in normal tissue complications as large volumes of adjacent tissues receive high doses. The current focus is on treating tumors with escalated doses (>75 Gy) with highly accurate prostate localization and substantially smaller planning margins. Our efforts have been directed toward relating the uncertainty in prostate location to variations in TCP and NTCP after registration with the *Minimax* and *GFW Minimax* algorithms.

METHODS AND MATERIALS

The *Minimax* algorithm was discussed extensively in another paper (22). We shall introduce the essential steps of the algorithm and discuss the changes and extensions that were made since it was first introduced.

The Minimax algorithm

The algorithm has two steps that run iteratively to determine portal image segmentation and the registration parameters. Portal images are segmented into two regions: bone and background. The intensities in these regions are assumed to be drawn from two different distributions. The *Max Step* estimates the segmentation of the portal image into “bone” and “no-bone” (background) based on *a posteriori* estimates of the pdf. The *Min Step* then estimates the joint densities by using the segmentation labels computed in the *Max Step*. This (*Max*, *Min*) process continues until convergence. Within the framework, we use a Markov Random Field (MRF) strategy incorporating line processes [as in (23)] to model pixel-to-pixel correlations and also the boundaries between the “bone” and “no-bone” regions.

The mathematical setup is as follows (24): All images (3D and 2D) are converted to a vectorized form where each individual pixel or voxel can be indexed by a one-dimensional parameter i . First, let $\mathbf{G} = \{\mathbf{g}_i, \forall i = (1, \dots, (I \times J \times K))\}$ be a homogeneous random field with pdf, $p_{\mathbf{G}}(\mathbf{G})$ [abbreviated as $p(\mathbf{G})$] with each outcome $\mathbf{G}$ being a 3DCT image of size $I \times J \times K$. Next, if $\mathbf{T}$ is a 6-parameter vector representing values for the three possible translations and three possible

rotations in a rigid 3D transformation, we can let each outcome $Y(T)$ of the random field $\mathbf{Y}$ ($\mathbf{T}$) = $\{\mathbf{y}_i(T), \forall i = (1, \dots, I \times J)\}$ be an image of size $I \times J$ pixels that is formed by taking a projection through the 3DCT image and is referred to as a DRR. When T is conditioned on the image information, it is also a random vector ($\mathbf{T}$). Finally, we let $\mathbf{X} = \{\mathbf{x}_i, \forall i = (1, \dots, I \times J)\}$ be a homogeneous random field also with pdf $p(X)$, whose each vectorized outcome X is a particular view MV portal image taken of the same patient that contains $I \times J$ pixels. The portal image and the DRR are usually of the same size, but if they are not, we evaluate the various entropy terms $[P(\cdot) \ln P(\cdot)]$ in Eq. 2] on the overlapping regions of the two images. We assume that the pixels in each of the random fields are identically and independently distributed (*iid*).

Thus, the pdf of the random field $\mathbf{X}$ can be factored as $p_{\mathbf{x}}(X) = \prod_i p_{x_i}(x_i)$. For notational simplicity, we shall now write $\mathbf{x}(i)$ as $\mathbf{x}_i$ and $\mathbf{y}(\mathbf{i}, \mathbf{T})$ as $\mathbf{y}_i$. Here, segmentation information is incorporated into the problem of matching each portal image to a related DRR by considering the joint density function $p(x_i, y_i)$ as a mixture density. Indicator variables with values of 0 or 1 signifying no-bone and bone classes are introduced at each pixel position to classify the content. Line processes based on edge information and intensity correlations between neighboring pixels are introduced at this stage to constrain the usually ill-posed problem of segmentation and to achieve robustness with respect to noise. Consequently, for any portal image p , we can realize a segmentation matrix that can be considered to be one outcome of a $N \times N$ random field $\mathbf{M}_p = \{\mathbf{m}(\mathbf{i})\}$, for $i = 1, \dots, N^2$. For our purposes, at each spatial position i each random variable $\mathbf{m}$ is labeled as either “bone” or “no-bone”. We iteratively solve for pdfs related to the segmentation of any and all portal images p first and then use them to estimate a best overall transformation T between the planning CT space and the treatment space using a *Minimax* entropy strategy. This can be summarized as follows:

The Max Step:

$$P^k = [P^k(M_p), p=1 \dots N] \quad (1)$$

$$P^k(M_p) = \arg \max_{P(M_p)} \left[- \sum_{M_p} P(M_p) \ln P(M_p) + \sum_{M_p} P(M_p) \ln P(M_p | X_p, Y_p(T^{(k-1)})) \right] \quad (2)$$

where $P^k(M_p)$ is the pdf for a segmentation M_p which is sampled from a possible set of segmentations for each portal image, given the current rigid transformation set: T . The iteration number is represented by k , and p is the index over the portals being segmented (typically 1, 2, or 4). X and Y are the one-dimensional MRFs drawn from the portal image and the 3DCT projected DRR related to it respectively. This inference assumes that pixel intensities are not independent and identically distributed (*iid*), but are correlated to their neighbors. The solution to Eq. 2 is as follows:

$$P_i^k(a) = \left(\frac{P_i^{(k-1)}(a) P_a^{(k-1)}(x_i, y_i)}{\sum_{b \in A} P_i^{(k-1)}(b) P_b^{(k-1)}(x_i, y_i)} \right) \quad (3)$$

Equation 3 estimates the probability that the segmentation class of the i th pixel is either “bone” or “no-bone”. The class labels are represented by a (or b) and are drawn from A which is the complete classification set. The density functions for the class labels are represented by $P^{k-1}_a(x_i, y_i)$, and are estimated using the *Parzen Windows* method.

The Min Step—Each portal image's registration with its corresponding DRR, at every iteration step k , produces a distinct transformation parameter set T_i^k . The global transformation set $\widehat{T}^k$ is a *statistical union* of these individual transformation sets:

$$\widehat{T}^k = T_1^k \cup T_2^k \cup \dots \cup T_N^k \quad (4)$$

where each parameter set is a vector of its weighted components: $T_i^k: \{\alpha_j t_j\}$, $0 \leq \alpha_j \leq 1$, $t_j: \{t_x, t_y, t_z, \theta_x, \theta_y, \theta_z\}$. Weighting was introduced because a particular pose estimates some parameters better than others. For instance, on registering the AP portal to its corresponding DRR, the parameters best estimated are t_x , t_y , and θ_z . The individual T_i values are computed iteratively as follows:

$$\begin{aligned} T_i^k &= \underset{T}{\operatorname{argmin}} H(M, X|Y) \\ &= \underset{T}{\operatorname{argmin}} \left(\sum_{a \in A} \left(\frac{1}{N^2} \sum_{i=1}^{N^2} P_i^k(a) \right) H_a(x, y) - H(y) \right) \\ &= \underset{T}{\operatorname{argmin}} F(T) \end{aligned} \quad (5)$$

where $H_a(x, y)$ is the joint entropy (of the DRR and portal) for class a , and N represents the dimension ($N \times N$) of the random field from which the portal images are sampled and $F(T)$ is the cost function to be minimized. We follow the optimization technique of *stochastic gradient descent* (19) adapted for inclusion of segmentation information. Transformation parameters are updated according to the following strategy until convergence, or until a preset number of iterations are reached.

$$\begin{aligned} \mathbf{I} &= \{(x_i, y_i) | x_i \in \mathbf{X}, y_i \in \mathbf{Y}, i=1 \dots N_1\} \\ \mathbf{J} &= \{(x_j, y_j) | x_j \in \mathbf{X}, y_j \in \mathbf{Y}, j=1 \dots N_j\} \\ \mathbf{T} &\leftarrow \mathbf{T} + \lambda \frac{d}{dT} F(T) \end{aligned} \quad (6)$$

where λ is the learning factor and $\mathbf{I}$ and $\mathbf{J}$ are randomly sampled sets of pixels used to estimate both the component density functions and joint entropy terms. Overall, in two iterative steps, this algorithm uses mixture densities to estimate pixel labels of bone and no-bone and arrives at an optimum transformation parameter set T .

Extensions to the algorithm

An efficient probability density estimation method—A crucial step in the *Minimax* algorithm is the computation of probability densities. In most imaging modalities pdfs are not easily predicted, but are estimated. The standard estimation methods are grouped under *parametric*, *semiparametric*, and *nonparametric* methods. A Gaussian is a standard example of a parametric pdf, whereas a finite mixture model such as a *mixture of Gaussians* is an example of a semiparametric pdf (25). However, in many cases, nonparametric methods are the models of choice because no prior assumptions about the forms of the pdfs are required. Examples are histograms, K-nearest neighbor method, and kernel-based estimators such as the *Parzen Windows* (26). Viola and Wells used the *Parzen* method in the context of their MI metric because it provides a very smooth estimate (19). However, smoothness is often achieved at a great computational expense because this method uses the full data set to compute estimates. Component density functions, $P_a^k(x, y)$, in the *Max Step* are estimated by the *Parzen* method as follows:

$$P_a^k(x, y) \approx \frac{1}{N^2} \sum_{x_i, y_i \in I} P_i^k(a) G_\psi(x - x_i, y - y_i) \quad (7)$$

where N is the sample size, and $G_\psi(\dots)$ is a Gaussian kernel with variance ψ and (x, y) is the reference point at which the density is estimated. The function interpolates between the sample points, with each point contributing an amount proportional to its distance from (x, y) . It is apparent that the computation tends to be intensive if the sample set is large. Another constraint when using the *Parzen* method is that the sample set used to represent the density should not be the set from which the reference points are sampled. If N_1 and N_2 are the two sets, then at every point in set N_2 we need to calculate the linear combination of N_1 window functions, making the total $N_1 \times N_2$ computations. This computation becomes prohibitively large with increasing N_1 and N_2 .

In the current project, registering $512 \times 512 \times 400$ sized 3DCT datasets to multiple portal images has proved to be highly time-consuming and takes approximately 10 min on a personal computer (2.4 GHz). This prompted us to look at computational speedup strategies. We replaced the *Parzen* method with the *Support Vector Method (SVM)* as suggested by Vapnik and Mukherjee (27) for estimating the density. The SVM method recasts this as a standard optimization problem which is then solved with less computational expense. We set up the optimization problem as follows: Let $F_l(x) = 1/l \sum_{i=1}^l \theta(x - x_i)$ be an approximation to the distribution function corresponding to $p(x)$, where $\theta(\cdot)$ is the Heaviside function. As density estimation problems are known to be ill-posed (27), we introduce a regularization function $\psi(p)$, such that

$$\psi(p) = \|p\|^2 = \sum_{i=1}^l \beta_i K_h(x, y) \quad (8)$$

We minimize this functional subject to the following constraints:

$$\begin{aligned} \max_i \left| F_l(x) - \int_{-\infty}^x p(t) dt \right|_{x=x_i} &\leq \varepsilon_l \\ \beta_i &\geq 0, \sum_{i=1}^l \beta_i = 1 \end{aligned} \quad (9)$$

where ε_l is a regularization parameter, $K_h(\dots)$ is a non-negative kernel of width h , and ε_l are nonuniform weighting coefficients. Only a few of the β_i are nonzero and the x_i corresponding to those nonzero β_i are called the *support vectors* (27). A judiciously chosen kernel function will have the smallest number of support vectors. Consequently, the support vector method of density estimation is analogous to the *Parzen Windows* method, but with a sparser data set, and consequently, a faster convergence. We implemented this in a MI framework earlier and discovered that the SVM method used approximately one-third the data and was approximately 2.5 times faster than the *Parzen Windows* method (28). We later included it as part of our *Minimax* algorithm.

Registration with multiple variable FOV portal images

In 3DCRT, the therapy beam is shaped to conform to the projected prostate shape, and portal images acquired on the electronic portal imaging device (EPID) do not represent a full FOV with all bony structures used to assess positioning accuracy. In IMRT, an incident beam may

only deliver treatment to a subset of the target volume, further decreasing the value for registration purposes of transmission EPID images acquired with the therapy beam. In such cases, it is imperative that a registration algorithm should detect discernable structures within this truncated window (RFOV images) and accurately perform the registration. We introduce a window function $W(X_i, \omega(r, l))$ which defines a subset of the portal image, with r and l representing the size and location of the window. Let S represent a segmentation map in the window. This segmentation map in the portal window must be registered to one of a set of similar windows in a projected DRR containing a similar segmentation distribution. The conditional probability distribution of the portal window is:

$$(P(W(X_i, \omega) | S_i) = \Psi(W(X_i, \omega); \mu, \sigma) \quad (10)$$

where $\Psi(.,.,.)$ is a distribution of the intensities in the window with a mean μ and a standard deviation σ , and as in the previous section, “The *Minimax* algorithm,” M is a particular overall segmentation map of which S is a subset. It follows from Bayes' theorem

$$P(M | W(X_i, \omega), S_i) = \frac{P(W(X_i, \omega), S_i | M) P(M)}{P(W(X_i, \omega), S_i)} \quad (11)$$

The modified *Max Step* may be expressed as follows:

$$P^k(M_i) = \arg\max_{P(M_i)} \left[- \sum_{M_i} P(M_i) \ln P(M_i) + \sum_{M_i} P(M_i) \ln P(M_i | W(X_i, \omega), Y_i(T^{k-1}), S_i) \right] \quad (12)$$

where k is the iteration number. This is similar to Eq. 2 with modifications to accommodate the reduced information in truncated windows. The function estimated in the previous step is used in calculating the transformation T in the *Min Step*. Mathematically,

$$\hat{T} = \arg\min_T \left[\sum_{i=1, \dots, 4} H(M_i, W(X_i, \omega), S_i | Y_i) \right] \quad (13)$$

In our modified algorithm we used RFOV portals with sparser sets of data points, but this drawback was offset by the addition of extra portal images ($n = 4$).

Gradient feature weighted intensity matching: GFW Minimax

Sparse field registration is accurate but susceptible to noise, whereas dense field registration is more robust to noise and other factors, but can be computationally expensive and sometimes less precise. A key development in our efforts to enhance the *Minimax* registration was to combine the sparse and dense field approaches. The advantages of each could be seized, while avoiding the liabilities. In our efforts we were guided by some earlier approaches (29,30). The implementation of this method proceeds along the lines described earlier in the section, “The *Minimax* algorithm,” but with the incorporation of sparse field information. At a given transformation parameter set T , each portal image and its corresponding DRR are resized to a preset scale γ and contrast enhanced. Gradient operators ($\nabla = \partial/\partial x + \partial/\partial y$) are applied to both images: $\nabla X_p(\gamma)$ and $\nabla Y_p(T^{(k-1)}, \gamma)$ and the edges thus recovered are sampled uniformly, depending upon the scale factor γ . At corresponding points in both images, angles (α) between these gradient vectors are computed as inverse cosines of the normalized scalar products of the vectors:

$$\alpha = \arccos \frac{\nabla X_p(\gamma) \cdot \nabla Y_p(T^{(k-1)}, \gamma)}{|\nabla X_p(\gamma)| |\nabla Y_p(T^{(k-1)}, \gamma)|} \quad (14)$$

The angles are incorporated into weighting factors as $w(\gamma) = (\cos(2\alpha) + 1) / 2$. The factors are subsequently multiplied with the minimum of the two gradient magnitudes: $\min\{|\nabla X_p(\gamma)|, |\nabla Y_p(T^{(k-1)}, \gamma)|\}$, to create a scalar variable $\Gamma(X_p(\gamma), Y_p(T^{(k-1)}, \gamma))$. Each contributing sample point's intensity is weighted with $\Gamma(\dots)$. After incorporating sparse field information, the new transformation parameter set in the *Min Step* is computed. Thus strong gradients have a greater emphasis and the corresponding points (typically edges and ridges of bony segments) drive the registration process. This mixed approach was particularly helpful with low-contrast portal images.

Influence of registration errors on TCP and NTCP

The algorithm that we found to be most accurate (*GFW Minimax*) was used to compensate for setup variations in patient positioning. The planned dose profiles were blurred and overlaid on the reference 3DCT image. The blurring was done to simulate positioning and organ (bladder, prostate, and rectum) location uncertainties between successive fractions, as was earlier done by van Herk *et al.* (31). Dose-volume histograms (DVH) which represent the cumulative absorbed radiation by a segmented organ were computed. Investigators have attempted to reduce DVH information to two simple quantities: the TCP and the NTCP (20,21). Current models that compute TCP and NTCP mainly rely on a factor called tumor clonogen radiosensitivity (SF_2) (21,32). SF_2 is defined as the fraction of tumor cells that survive a 2 Gy dose (33,34). In our computation of TCP and NTCP, we also included algorithm-derived variations in prostate position (35,36).

Implementation

Testing was done on both phantom and patient data sets.

Phantom data—Four 3DCT-to-portal registration algorithms were compared and contrasted using data obtained by imaging a bone-embedded-in-Plexiglas pelvic phantom. CT images of the phantom were acquired on a GE Lightspeed Spiral CT scanner (GE Healthcare, Waukesha, WI). Voxels were 1.0 mm in all dimensions. A volume rendering of the pelvis obtained from these data is shown in Fig. 1. Portal images (6 MV) were acquired on an amorphous silicon (aSi500, PortalVision; Varian Medical Systems, Palo Alto, CA) electronic portal imager (EPID) in the AP and LL directions. The sensitive active imaging area of the detector (array dimension) is $40 \times 30 \text{ cm}^2$. It has a 512×384 pixel (0.784 mm pitch) matrix. The portal images of the phantoms were acquired in 14 different combinations of translations or rotations relative to a fixed origin. This was performed by placing the phantom on the treatment couch, and moving the calibrated couch and gantry and the EPID imager accordingly. The calibrated movements consisting of 6 parameters (3 translations and 3 rotations) were recorded as ground truth. The details of the combinations are given in Table 1.

The four different automated or semiautomated 3DCT-to-2-portal rigid image registration approaches used to estimate the setup variation from the planning data (3DCT) to the treatment environment were:

- i. Estimates of bony ridge information as described in (16).
- ii. Intensity-based normalized MI (37).
- iii. The *Minimax* algorithm (see the section, “The *Minimax* algorithm”).

- iv. The *GFW Minimax* algorithm (see the subsection “Gradient feature weighted intensity matching: GFW Minimax”).

Patient data—An important goal was to apply our fully automated algorithm to estimate actual patient setup variations. We acquired unique sets of data for 8 subjects that included a 3DCT reference image (with 1 mm^3 voxels) at the initial planning day using our GE Lightspeed Spiral CT scanner. Subsequently, for 7 weeks, EPID images (AP and LL) were acquired weekly using a Varian EPID system or our film-based system. On these days, volumetric 3DCT images were also acquired to develop gold standard plans. For all acquisitions, the patient was constrained in a soft foam immobilization system, with the toes aligned vertically, in accordance with our clinical protocol and using the same parameter settings as Day 1. The methodologies for phantom and patient testing were essentially similar, except that Gilhuijs' method was not used on patient data. The MI algorithm served as a benchmark for comparison.

Dosimetry data—The 3DCRT patients received a dose of 75.6 Gy in 42 fractions, each nominally at 1.8 Gy with a dose margin of 10 mm around the prostate. CT images were acquired at resolutions of $0.9\text{ mm} \times 0.9\text{ mm} \times 1.0\text{ mm}$. The prostate, rectum, and bladder were segmented and the CTV and PTV were drawn by a radiation oncologist. The dose distributions were determined for six 18-MV photon beams. The plans were generated at 2.0 mm resolution in all directions using a 3D planning system (Theraplan Plus 3.7, Nucletron, Veenendaal, The Netherlands). Once the prostate location uncertainties were known, the pdfs for the prostate dose ($p(D)$) were computed by interpolation for each location and the results archived on the computer. Dose plans were spatially scaled around the prostate to simulate narrower margins between 4 mm and 10 mm, and the process of determining $p(D)$ for various positions was repeated and finally the DVH, TCP, and NTCP outcomes were computed.

RESULTS

The data used in this study consisted of phantom and patient data. When registering 3DCT data with four portals, the latter were simulated from phantom data. When comparing various segmentation/registration algorithms, we used 3DCTs and megavoltage portals that were obtained from patients and a phantom.

Registration using four portal images

A set of four simulated portal images were registered to 3DCT phantom data. The portal images of pixel size 1 mm were created by projecting through the phantom 3DCT. Two were the AP and LL portals (0° and 90°), and the other two were posterior oblique (135° and 215°). Accordingly, there is no duplication of information in any direction. Figure 2(a–d) shows the final segmentation in all four directions.

Figures 3a and 3b show results of registering two and four portals with initial misalignments of 10 mm and 10° in the x-y plane, in the presence of increasing Gaussian noise. Using four portals resulted in an error reduction of 30–50%. In both figures, the abscissae show noise in terms of the standard deviation. The addition of Gaussian noise of standard deviation σ implies that 34.13% of the additive noise will have gray level values in the range $[0, \sigma]\%$ of the maximum intensity of the image (8 bits, 255 gray levels in this case) (38). To estimate the effect of noise in portals, varying amounts of it were added to the images and signal-to-noise (SNR) ratios were computed. These portals were then registered to the 3DCT data and the absolute errors were noted. With no initial misalignment, an error-free run should converge to 0 mm. Figure 4 is a plot of SNR vs. the absolute translation error for registration with two and four portals. In practice, SNR values vary widely. Hilt *et al.* cited a value of 0.97 for a pelvic portal image which was then enhanced to 42.84 after intensity correction and noise reduction

(39). In this experiment, using four portals resulted in a reduction of registration error. The major problem in using four portals was the computation time which was almost 1.5 times that required for two portals.

Registration using variable FOV portal images

Four portal images (256×256 pixels, pixel size: 1 mm) with varying FOV (RFOV) were simulated by placing a window centered at the prostate and then sequentially shrinking it. The resulting images captured a range of structures from the center of the image to the full feature set. Figure 5 displays plots of absolute translation and rotation errors vs. different window sizes. At a window size in the vicinity of 175 pixels (6 cm FOV), both plots make a transition beyond which the reduction error is not significant. We assume that a window of 175 pixels captured most of the tangible features in the images and a wider window did not necessarily add more information. However, we need to test this hypothesis more rigorously on a larger data set. The registration with four RFOV (35% reduction in size) portal images has converged to the true transformation values in a time frame comparable to the case when two FFOV portals were used. However, when four RFOV portals were used, the registration time was approximately 1.5 times longer than the situation when two FFOV portals were used, as previously noted.

Comparison of various 3DCT to multiple portal image registration algorithms using phantom data

Data consisting of 3DCT images and AP and LL portal images were acquired by imaging a bone-embedded-in-Plexiglas pelvic phantom. In this experiment, the ground truth data ($\mathbf{T}_{gold}$) is assembled from the true estimates of the position settings as given in Table 1. The estimates of the six rigid mapping parameters using previously described algorithms are recorded as setup variation vectors $\mathbf{T}_{alg}$. For statistical comparisons, we used two factors: *Algorithm Type* consisting of four different possibilities, *Setup Variation Parameters* consisting of 3 translations (t_x, t_y, t_z in voxels) and 3 rotations ($\theta_{xy}, \theta_{yz}, \theta_{zx}$, in degrees). Dependent variables are error magnitudes between any one of the gold standard parameters and the matching algorithm-predicted parameters (e.g., $\varepsilon_{t_x} = |t_{x-gold} - t_{x-arg}|$). A sample set of errors (ε_{t_x}) for one position setting is presented in Table 2. The results of using MI and the *GFW Minimax* algorithms to map several regions visualized and marked by a radiologist on the AP portal images to the candidate matched AP DRR are illustrated in Fig. 6a. A chart summarizing the results from applying the four algorithms to all 14 positions listed in Table 1 is shown in Fig. 6b. It displays the percentage improvement in error $((\varepsilon_{MI} - \varepsilon_{alg}) / \varepsilon_{MI})$ for each algorithm when compared with MI. Of all metrics, MI's registration showed the largest deviation from the gold standard parameters. The dense field *Minimax* method and the bony ridge based methods (Gilhuijs' technique) fared better, but the *GFW Minimax* method performed the best by a significant margin for all translations and rotations ($p < 0.05$ corrected for multiple comparisons). The number of iterations (series of *Max* and *Min* steps) was constrained to be within 10. If the algorithm did not converge by this number, it would imply that it was not properly initialized, and one or more conditions such as the initial transformation parameters, source to patient or patient to EPID distances were not correctly set. However, in all the successful instances, the algorithm converged between 3 to 7 iterations for both versions of the *Minimax* method.

Comparison of various 3DCT to multiple portal image registration algorithms using patient data

In this experiment, we estimated the vector $\mathbf{T}_{gold}$ by performing 3D-to-3D registration of planning and treatment Day 3DCT images using normalized MI. To compare candidate 3DCT-

to-dual-portal registrations with this gold standard, two 3DCT-to-2-portal rigid registrations were performed in sequence for each of the above algorithms for each patient:

- i. A registration of the planning Day 3DCT to the two treatment day portals, from which the forward setup variation parameters $\mathbf{T}_{alg-setup}$ are estimated.
- ii. A registration of treatment day portals to treatment Day 3DCT data, which estimates the position variation between the treatment couch and the 3DCT scan (performed in a separate room).

Composing the forward setup variation $\mathbf{T}_{alg-setup}$ with the inverse of the treatment day position variation $\mathbf{T}_{alg-comp}^{-1}$ allows us to form an algorithm-specific rigid registration error from the gold standard that we use as our dependent variable for testing:

$$\varepsilon_{T-alg} = \left\| \mathbf{T}_{gold} - \left[\mathbf{T}_{alg-setup} \circ \mathbf{T}_{alg-comp}^{-1} \right] \right\|^2 \quad (15)$$

where $\circ$ indicates matrix multiplication. To compare algorithms, we followed the same procedure used in the subsection “Phantom data.” In this experiment, we did not use Gilhuijs’ method because the bony landmarks in the portal images were not clearly delineated, and consequently, a considerable amount of contrast adjustment of the images would be required which detracts from the automated nature of the algorithms under comparison. For each of the two new, nonstandard algorithms (*Minimax*, *GFW Minimax*) we computed the percentage improvement of the registration compared with that produced by the MI method as: $((\varepsilon_{MI} - \varepsilon_{T-alg}) / \varepsilon_{MI})$. The individual ε ’s were obtained via comparison to the gold standard. Statistically significant differences were found between the algorithms with MI showing the most error. Improvement was seen with the *Minimax* approach, and even greater gains were seen when using *GFW Minimax*. Figure 7a shows example results from 1 patient comparing traced bony ridges transferred from a projection through the 3DCT data to the AP portal image, using MI and *GFW Minimax* approach, to a tracing of the same structure on the portal image. Figure 7b summarizes the key findings here by plotting the percentage improvement over MI (see above) for the *Minimax* and *GFW Minimax* algorithms for 8 patients, compared across 4 (out of 6) weeks of treatment. This plot clearly indicates the improvement of the *GFW Minimax* algorithm over the other approaches ($p < 0.05$). The number of iterations when using the *GFW Minimax* method ranged between 4 to 7.

Effect of setup variations on treatment plan delivery

The uncertainties (standard deviation σ mm) in patient setup were computed after performing registration with the algorithm that gave the lowest errors: *GFW Minimax*. To understand the impact of these errors on therapy, parameters such as the TCP and NTCP were calculated using a standard linear-quadratic (LQ) model (21). Different margins (M), ranging from 1–10 mm were simulated by shrinking the original dose plan about its isocenter. TCP and NTCP were calculated for the patients described in the subsection “Patient data” where weekly portals and CT scans (Day 7, Day 14, etc.) had been acquired in addition to the typical Day 0 CT. Bony structures as well as the segmented prostate, bladder, and rectum can be identified in each of the CTs shown in Fig. 8. Such information is potentially useful to compensate for the setup variation, and to better center the dose field on the prostate. The observations provided here are illustrative of the setup uncertainty occurring over all the fractions of therapy. The effect of such uncertainty is to make the dose distribution diffuse (40).

Contour plots of prostate TCP and rectum and bladder NTCP values in the (M , σ) domain are shown for one of these patients in Fig. 9. As illustrated in the Day 0, Day 7 CTs of Fig. 8, the prostate is shifted relative to the PTV during every dose fraction (or stage). The positions of

the prostate from one stage to the next, related to patient positioning and internal organ motion issues, are generally independent from stage to stage. TCP is relatively insensitive to σ for the $M = 10$ mm currently used for external beam radiation therapy. However, with margin reduction the TCP becomes quite sensitive to setup error. Rectal NTCP and bladder NTCP are relatively insensitive to σ , because these organs can move either toward, or away from, the high dose region during the fractions of external beam radiation therapy. Thus NTCP is most sensitive to margin M . Although the maps are essentially the same for all the patients in current M and σ ranges, for tighter M and improved σ (i.e., reduced setup error) features of the maps become more patient-specific.

DISCUSSION

Although conformally planned escalated dose treatments can be beneficial for organ-confined prostate cancer (41,42), the poor quality of portals in the treatment environment as well as the lack of robust, automatic registration of reference to treatment images has hindered treatment setup verification. Accurate assessment of treatment plan delivery is thus difficult. Neglecting such problems could lead to rectal or bladder injury or insufficient dose delivered to the prostate cancer. This is particularly critical for implementation of IMRT plans which have steep dose gradients at the beam edges. Hence, a crucial first step for effective radiotherapy is correct patient positioning. Toward this goal we introduced and improved upon a novel automated iterative registration and segmentation method called the *Minimax* algorithm.

Initially, the *Minimax* algorithm was a purely intensity-based metric. We extended it to include a combination of intensity and feature-based measures (*GFW Minimax*). We then compared our method to two other popular methods: MI and Gilhuijs' method. Our mixed approach gave the best results when registering patient data, whereas a purely feature-based approach was not very successful because of limited contrast in the portal images. However, with phantom data, both feature-based and mixed approaches worked very well, with the latter outperforming the former by a slight margin. This was due to the fact that in a phantom image formed from the pelvic bones, the only noticeable aspects were the edges and ridges. Differences in tissue contrast were negligible, which resulted in the purely intensity-based methods (MI and intensity-based *Minimax*) not doing all that well.

The other aim of this study was to effectively and efficiently register multiple portal images to 3DCT volume data. We did so using data drawn from simulations, phantom images, and patient images. Using simulations we verified that using four vs. two portal images reduces registration error by 30–50%, albeit at some computational expense. It would be instructive to correlate the reduction of error to the number of portal images used for registration. Although not entirely analogous, in a fully 3D-to-3D registration the number of views employed for registration is not a constraint. However, instead of pushing the computation to its limits, the registration process can be terminated once the point of diminishing returns is reached. In this case, that would be the maximum number of projections, beyond which the accuracy would cease to improve.

We also experimented with RFOV images, as in many cases the clinical images do not contain a full set of features. As is expected, registration with images with wider FOV results in lower errors. However, there was a transition point beyond which the reduction of error was not significant. In the current case, that was around a window size of 175 pixels (FOV of 6 cm). We believe that a stage was reached wherein most of the significant details in the images are now present, and consequently, any further widening of the window will not bring in more features. This conclusion needs to be tested on a larger set of images.

Once we compared algorithms and chose the optimum one (*GFW Minimax*), we decided to explore the correlation between registration errors or uncertainty in prostate position and the variability in TCP and NTCP. We should note that although registration errors contribute significantly to the uncertainty in prostate location, other sources of error are internal organ motion and inherent errors in the therapy machine. Our algorithm does not account for prostate motion as it only utilizes rigid pelvic bony landmarks. Our results demonstrate that if the position uncertainty is reduced to ~1 mm, the dose margins can be scaled down substantially from the current 10 mm to 4 mm, without adversely affecting TCP and NTCP. This emphasizes the crucial role played by imaging techniques in the administration of radiotherapy.

A logical extension to the work presented in this paper is to incorporate fully 3D-to-3D nonrigid registration into our algorithm. Our improvements and extensions were all based on rigid registration that cannot accommodate internal motion relative to the pelvic structure. This requires images superior in quality to the portal images. The evolving trend of daily conebeam 3DCT data acquisition would provide images with good soft tissue contrast, but will carry its own problems and challenges and will amplify the need for a fast 3D automated segmentation and registration metrics.

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Fig. 1. Three-dimensional rendering of the phantom data used for simulating portal images in various configurations.

Fig. 2. Registration with four simulated portals (a–d). Segmentation was done implicitly by the *Minimax* algorithm. White pixels represent the bony tissue.

Fig. 3.

Errors in registering two and four simulated portals to three-dimensional computed tomographic data. Initial misalignments of 10 pixels in the xy plane (a) and 10° in the z direction (b) were introduced. The abscissae represent the standard deviation of the noise as a percentage of the maximum intensity in the image. Using four portals (solid line) resulted in a 30–50% reduction in the error compared with two portals (dashed line).

Fig. 4. Plot of the signal-to-noise ratio (SNR) vs. the absolute translation error. The dashed and solid lines represent errors in registration with two and four portals respectively. Using four portals (solid line) has consistently lowered registration error compared with two portals (dashed line).

Fig. 5.

Absolute translation and rotational errors vs. different window sizes for four portals. The full size of the portal image is 256×256 pixels. There is a transition at the 175 pixel window size after which the reduction in error is not significant.

Fig. 6.

Three-dimensional computed tomography to two portal rigid image registration: algorithm comparisons using a phantom. (a) Illustrative example: tracings of several bony ridges done on an anterior-posterior portal image and mapped to a matched projection through three-dimensional computed tomographic image using Mutual Information (MI) (white-dashed) and *GFW Minimax* (white-solid). (b) Summary plot of the percentage error difference between the estimate obtained using one of the three algorithms (*Minimax*, *GFW Minimax*, and Gilhuijs) and MI; e.g., if the error of the algorithm was 0.8 mm and the error using MI was 1.0, the percentage error is -20%. All three methods showed statistically significant improvements over MI ($p < 0.05$ corrected for multiple comparisons). *GFW Minimax* and Gilhuijs' methods showed statistically significant improvement over *Minimax*. w.r.t. = with respect to.

Fig. 7.

Three-dimensional computed tomography to two portal registration: algorithm comparisons using $n = 8$ patients (portal data acquired weekly at 5 treatment fractions). (a) Illustrative results from 1 patient: solid-white = tracings of several bony ridges on anterior-posterior portal; also shown are tracings of the same structures on a projection of the three-dimensional computed tomographic volume at a similar position, mapped back to the portal image via Mutual Information (MI) algorithm (dashed-white) and *GFW Minimax* algorithm (dot-dash-black). (b) Percentage error difference between the estimate obtained using *Minimax* or *GFW Minimax* and MI; e.g., if the error of the algorithm was 0.8 mm and the error using MI was 1.0, the percentage error is -20%. Both methods showed significant improvements over MI ($p < 0.05$).

corrected for multiple comparisons), and *GFW Minimax* showed significant improvement over *Minimax*. w.r.t. = with respect to.

Fig. 8.

Influence of setup errors on outcome of therapy. Computed tomograms at Days 0 (initial day) and 7. The numbers on the contours represent percentages of the target dose delivered to the enclosed regions. Panel (a) shows the segmented computed tomogram at Day 0 and the corresponding dose plan contours (solid-white). The prostate (solid-black) is centered in the dose plan. In panel (b), corresponding to Day 7 of external beam radiation therapy, due to setup error, more of the rectum (dashed-black) is in the high-dose region of the Day 0 plan, while the bladder (dashed-white) has moved out of the high-dose region. The prostate is no longer centered in the dose plan.

Fig. 9.

(a) Tumor control probability contours for the prostate; (b) and (c) normal tissue complication probability contours for the rectum and bladder, respectively. The results of uncertainties in organ location (σ mm) for external beam radiation therapy at different dose margins (M mm) are displayed. Patient data were used with the *GFW Minimax* algorithm to compute the position uncertainties. Results show that with a substantial reduction in the uncertainty, dose margins can be lowered to achieve high tumor control probability and low normal tissue complication probability values.

Table 1

The phantom was oriented and imaged in 14 different positions. At each position, portal images in the AP and LL directions were obtained. Translations (measured in mm) in the x, y, and z directions are denoted by t_x , t_y , and t_z respectively. Rotations (in degrees) in the xy, yz, and zx planes are denoted by θ_{xy} , θ_{yz} and θ_{zx} respectively.

Param	1	2	3	4	5	6	7	8	9	10	11	12	13	14
t_x	0	2	0	0	20	0	0	10	0	0	0	0	0	-4
t_y	0	0	2	0	0	20	0	10	0	0	0	0	0	6
t_z	0	0	0	2	0	0	20	10	0	0	0	0	0	-3
θ_{xy}	0	0	0	0	0	0	0	0	2	5	0	0	0	0
θ_{yz}	0	0	0	0	0	0	0	0	0	0	5	0	0	0
θ_{zx}	0	0	0	0	0	0	0	0	0	0	0	2	5	-5

Table 2

A sample set of results obtained from using four registration metrics on phantom data from one of the experiments listed in Table 1

Param	MM1	MM2	MI	G
t_x	1.5	-1.2	1.8	-1.3
t_y	1.8	-1.6	-2.0	1.8
t_z	1.4	1.2	1.9	1.5
θ_{xy}	1.6	1.1	-1.9	1.3
θ_{yz}	1.7	1.2	-1.8	-1.4
θ_{zx}	-1.6	1.2	1.8	1.3

The metrics used were *Minimax* (MM1), *GFW Minimax* (MM2), Mutual Information (MI), and Gilhuijs' method (G). Translations (in mm) in the x , y , and z directions are denoted by t_x , t_y , and t_z and rotations (in degrees) in the xy , yz , and zx planes are denoted by θ_{xy} , θ_{yz} , and θ_{zx} respectively. The values in the table represent deviations from true values, which were $t_x = t_y = t_z = 10$ mm and $\theta_{xy} = \theta_{yz} = \theta_{zx} = 0^\circ$. MM2 resulted in the smallest deviations from true values.