A Bayesian approach to real-time 3D tumor localization via monoscopic x-ray imaging during treatment delivery

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Purpose: Monoscopic x-ray imaging with on-board kV devices is an attractive approach for real-time image guidance in modern radiation therapy such as VMAT or IMRT, but it falls short in providing reliable information along the direction of imaging x-ray. By effectively taking consideration of projection data at prior times and/or angles through a Bayesian formalism, the authors develop an algorithm for real-time and full 3D tumor localization with a single x-ray imager during treatment delivery.

Methods: First, a prior probability density function is constructed using the 2D tumor locations on the projection images acquired during patient setup. Whenever an x-ray image is acquired during the treatment delivery, the corresponding 2D tumor location on the imager is used to update the likelihood function. The unresolved third dimension is obtained by maximizing the posterior probability distribution. The algorithm can also be used in a retrospective fashion when all the projection images during the treatment delivery are used for 3D localization purposes. The algorithm does not involve complex optimization of any model parameter and therefore can be used in a “plug-and-play” fashion. The authors validated the algorithm using (1) simulated 3D linear and elliptic motion and (2) 3D tumor motion trajectories of a lung and a pancreas patient reproduced by a physical phantom. Continuous kV images were acquired over a full gantry rotation with the Varian TrueBeamTM on-board imaging system. Three scenarios were considered: fluoroscopic setup, cone beam CT setup, and retrospective analysis.

Results: For the simulation study, the RMS 3D localization error is 1.2 and 2.4 mm for the linear and elliptic motions, respectively. For the phantom experiments, the 3D localization error is < 1 mm on average and < 1.5 mm at 95th percentile in the lung and pancreas cases for all three scenarios. The difference in 3D localization error for different scenarios is small and is not statistically significant.

Conclusions: The proposed algorithm eliminates the need for any population based model parameters in monoscopic image guided radiotherapy and allows accurate and real-time 3D tumor localization on current standard LINACs with a single x-ray imager. © 2011 American Association of Physicists in Medicine. [DOI: 10.1118/1.3598435]

Key words: Bayesian, real-time, tumor localization, x-ray imaging

I. INTRODUCTION

Intrafractional organ motion is one of the major uncertainties in modern cancer radiotherapy. It limits the amount of radiation dose that can be safely prescribed to the patient without causing severe damage to normal tissues.¹ A solution to this problem is real-time tumor tracking, which dynamically targets the tumor with the radiation beam, allowing a reduction in the volume of healthy tissue exposed to a high dose. A prerequisite for effective tumor tracking is a precise knowledge of the 3D tumor location in real time.

The advent of on-board x-ray imaging systems on modern LINACs has made real-time tumor localization possible.^{2–5} Ideally, stereoscopic imaging (i.e., two simultaneous radiographic images acquired at oblique angles) is required to accurately locate the 3D tumor position. Several commercial LINAC-based imaging systems have this capability, e.g., the Novalis Tx system and the Mitsubishi/Hokkaido RTRT system. However, due to their complicated design and a higher

capital cost, these room mounted x-ray imaging systems are not widely used in the clinic. In addition, they have a small field of view and low imaging efficiency due to a large imager-patient distance. The current standard and most prevalent on-board imaging system is a single gantry-mounted kV x-ray imager, which is orthogonal to the MV treatment beam. Although stereoscopic imaging based on the kV and MV imagers is possible under some favorable conditions,^{6–9} several practical factors make it less straightforward for clinical applications, e.g., the reduced contrast in MV images, invisibility of the tumor or fiducial markers due to partial or complete blockage by the multileaf collimators during beam modulation.¹⁰ On the other hand, the kV x-ray images have much better contrast and do not suffer from the issue of blocked anatomy. Therefore, it is desirable to be able to estimate the 3D tumor position from a single x-ray imager during treatment delivery.

There have been a few studies that attempt to estimate the 3D tumor motion from monoscopic x-ray imaging. Marchant

*et al.*¹¹ estimated the superior-inferior (SI) motion using the projection data over a full gantry rotation and then estimated anterior-posterior (AP) and left-right (LR) motions using images of a 20° arc of when the imager was perpendicular to the corresponding direction. Since multiple images over an arc are needed, the method is retrospective and does not achieve real-time localization. Becker *et al.*¹² improved the algorithm by first labeling the projection images based on the breathing phase of the fiducial marker and then back-projecting the fiducial position from images of similar phase. Since the method relies on phase binning, it is susceptible to errors if the patient's breathing pattern is irregular during the image acquisition or treatment delivery. Estimation of the 3D tumor motion with monoscopic imaging is also possible using model-based methods for lung cancer radiotherapy,^{13–17} where implanted fiducial markers are not necessary. These methods are based on the 3D tumor or lung motion characteristics acquired during patient simulation or before each treatment fraction and then updated during treatment delivery.

A probability-based method to estimate the 3D tumor motion based on a single imager has been proposed and its applications were demonstrated through a simulation study,¹⁸ permitting real-time tumor localization. The main drawback of the approach is the assumption of a 3D Gaussian probability density function (PDF) for the underlying tumor motion. The Gaussian PDF is symmetric and unimodal (i.e., with one local and one global maximum). However, it is evident that for many anatomical sites, the tumor motion does not have this simple feature. For instance, for respiration-induced tumor motion, the duration for exhalation is usually longer than that for inhalation; the resultant 3D PDF would be asymmetric, i.e., more concentrated near exhalation. It is also possible for tumors to have hysteresis motion (tumors take different paths during exhalation and inhalation). For these tumors, the shape of the 3D motion PDF is an elliptical tube instead of an elliptical sphere. A Gaussian PDF is not an accurate representation of the tumor motion in many clinical cases, especially for tumors with complex motion trajectories. Another potential problem is the heuristic search in the presence of local minima during the optimization process, which could lead to suboptimal model parameters. In addition, the prostate motion is small and of very low frequency in most cases. For thoracic and abdominal tumors, however, the high-frequency oscillatory motion relative to the slow rotation of the on-board imager presents a major challenge for accurate 3D motion estimation.

In this work, we formulate the 3D localization problem from a single x-ray imager in a general Bayesian framework. In the Bayesian approach to motion estimation and tracking, one constructs the posterior PDF of the underlying motion based on the prior PDF and all available measurements. In principle, an optimal estimate of the motion can be obtained from the posterior PDF, which captures all the statistical information. For a simple linear Gaussian model, the well-known Kalman filter¹⁹ provides the optimal (and analytical) solution to the estimation problem. In a more realistic nonlinear and non-Gaussian environment, efficient estimation

methods have been proposed and widely adopted, such as particle filters.²⁰ In this work, we adopted a data-driven approach, where the motion probability distribution is constructed directly from the 2D tumor positions estimated from the projection images. The resultant 3D motion probability distribution is not restricted to any particular shape, but depends on the actual data. As such, it gives a more realistic representation of the underlying tumor motion characteristics and could potentially lead to more accurate 3D localization. It is applicable to both slowly moving tumors (e.g., in the prostate) and fast moving tumors in the thorax and abdomen. Furthermore, the method is versatile in that it allows the uncertainties associated with marker detection to be easily accommodated in the Bayesian framework. Another distinct advantage of this work is that there is no model parameter to be optimized for 3D localization purposes, and thus, it can be used in a “plug-and-play” fashion. All these desirable features of the proposed method facilitate its applications in routine clinical use.

In the following sections, we first present our Bayesian formulation of the 3D localization problem and show how it can be greatly simplified in order to find a meaningful solution. We then evaluate the algorithm using computer simulation with a realistic 3D linear and elliptic motions and rigorous experiments using a physical phantom with 3D tumor motion trajectories of actual patients. We present our results on simulation study and phantom experiments in Sec. III and furnish a broad scope of discussions in Sec. IV. We conclude our paper in Sec. V.

II. METHODS AND MATERIALS

II.A. Theoretical framework

We formulate the 3D localization problem in a Bayesian framework. In the following, we adopt the convention that bold letters are vector variables; all variables are deterministic variables unless specified otherwise. Given an x-ray projection image, the 2D projection of the tumor position onto the imager can be estimated. In reality, there are always errors associated with the estimation process, and this uncertainty can be represented by some probability distribution of the 3D tumor position. Given the estimated 2D position on the imager, we assume that the PDF of the 3D tumor position has the following form:

$$g(\mathbf{x}) = \alpha \cdot \exp[-||T(\mathbf{x}) - \mathbf{c}||_2^p / \beta^p], \quad (1)$$

where $\mathbf{x}$ is the 3D position of a point (a random variable) in the machine coordinate system and $\mathbf{c}$ is the estimated 2D tumor position (a random variable) on the imager in the imager coordinate system. $T(\cdot): \mathbf{R}^3 \rightarrow \mathbf{R}^2$ is a perspective projection which transforms the 3D position of a point to its 2D position projected on the imager in the imager coordinate system. For the sake of completeness, we give its expression here without proof, since it can be easily derived and has been presented elsewhere in the literature:⁸

$$c(1) = R \cdot \frac{-\mathbf{x}(1) \cdot \sin \theta + \mathbf{x}(2) \cdot \cos \theta}{r - \mathbf{x}(1) \cdot \cos \theta - \mathbf{x}(2) \cdot \sin \theta}$$

$$c(2) = R \cdot \frac{\mathbf{x}(3)}{r - \mathbf{x}(1) \cdot \cos \theta - \mathbf{x}(2) \cdot \sin \theta}$$

where $c(1)$, $c(2)$ are the two coordinates in the axial direction (along the axis of rotation on the imager) and the tangential direction (perpendicular to the axis of rotation on the imager and tangential to the gantry rotation), respectively; $\mathbf{x}(1)$, $\mathbf{x}(2)$, $\mathbf{x}(3)$ are the three coordinates in LR, AP, and SI directions, respectively, θ is the gantry angle, r is the source-to-axis distance, and R is the source-to-imager distance.

In Eq. (1), $\beta > 0$ is a scale parameter which is associated with the uncertainty in tumor detection, $p > 0$ is a hyper-parameter (i.e., it is not a parameter to be optimized during the localization), α is a normalization constant, and $\|\cdot\|_2$ denotes the l_2 norm of a vector (the reason l_2 norm is used for the difference vector $T(\mathbf{x}) - \mathbf{c}$ is to make it rotation invariant on the imager).

Note that the above PDF of the 3D tumor position has a uniform distribution along the ray line from the x-ray focal point to the point of interest. It is maximum along the ray line from the x-ray focal point to the estimated tumor position and decays exponentially away from this line.

Suppose we have a collection of N x-ray projection images acquired by a single imager (either rotational or fixed-gantry geometry) during patient setup. We can get the prior probability distribution, assuming all setup images are independent:

$$f_a(\mathbf{x}) = \gamma \cdot \prod_{i \in S} \exp \left[-\|T_i(\mathbf{x}) - \mathbf{c}_i\|_2^p / \beta_i^p \right] \quad (2)$$

where S is the index set for all the setup projection images, γ is a normalization constant, and the subscript a in $f(\mathbf{x})$ stands for a prior probability.

Suppose that we have acquired a new projection image during dose delivery and the estimated 2D tumor position on the imager is c_k , we write the likelihood function as following (since there is only one data sample, it is assumed to have the same functional form as the PDF in Eq. (1):

$$L(\mathbf{x}) = f(\mathbf{c}_k | \mathbf{x}) = \alpha \cdot \exp \left[-\|T_k(\mathbf{x}) - \mathbf{c}_k\|_2^p / \beta_k^p \right] \quad (3)$$

By combining Eqs. (2) and (3), we obtain the posterior probability distribution for the 3D tumor position at current time:

$$f_p(\mathbf{x} | \mathbf{c}_k) = \frac{f_a(\mathbf{x}) \cdot f(\mathbf{c}_k | \mathbf{x})}{f(\mathbf{c}_k)} = \gamma' \cdot \exp \left[-\sum_{i \in S} \left(\|T_i(\mathbf{x}) - \mathbf{c}_i\|_2^p / \beta_i^p \right) - \|T_k(\mathbf{x}) - \mathbf{c}_k\|_2^p / \beta_k^p \right] \quad (4)$$

where γ' is a normalization constant and the subscript p in $f(\mathbf{x})$ stands for posterior probability.

The observation variables of the Bayesian model are $\mathbf{c}_i$ estimated from all setup images and $\mathbf{c}_k$ estimated from current image. Given these variables, the maximum *a posterior* (MAP) estimator for the current tumor position is: $\hat{\mathbf{x}} = \arg \max_{\mathbf{x}} f_p(\mathbf{x})$ or

$$\hat{\mathbf{x}} = \operatorname{argmin}_{\mathbf{x}} \sum_{i \in S} (\|T_i(\mathbf{x}) - \mathbf{c}_i\|_2^p / \beta_i^p) + \|T_k(\mathbf{x}) - \mathbf{c}_k\|_2^p / \beta_k^p \quad (5)$$

In general, this nonlinear optimization problem can hardly be solved in real-time. However, we can greatly simplify the problem by making some reasonable assumptions. Since we are trying to estimate the tumor position at current time, intuitively it makes sense to assign larger uncertainties (or β) to the estimations obtained from images acquired earlier, while the estimate based on the current image should be associated with the smallest uncertainty. We can quantify this uncertainty in the setting of stochastic processes. In the special case of $p = 2$, the 2D likelihood functions are 2D Gaussian PDFs, which implies that the tumor motion when projected onto the 2D imager is a 2D Brownian motion. Considering the large source-to-axis distance (100 cm) and small tumor motion (~ 1 – 2 cm), this roughly corresponds to the assumption of an underlying 3D Brownian motion for the tumor. Then at the time of measurement, the current measurement could be considered exact (i.e., $\beta_k \rightarrow 0$); on the other hand, the uncertainty for previous measurements is proportional to the time elapsed since those measurements,²¹ i.e., $\beta_i^p \propto |t_k - t_i|$, where t_k , t_i are the time when the current image and i th setup image are acquired, respectively. In this work, we consider a generalized stochastic process in terms of the joint 2D likelihood functions that have the same property (i.e., uncertainty grows over time) for all $p > 0$. Finally, the MAP estimation problem in Eq. (5) becomes

$$\hat{\mathbf{x}} = \operatorname{argmin}_{\mathbf{x}} \sum_{i \in S} \|T_i(\mathbf{x}) - \mathbf{c}_i\|_2^p / |t_k - t_i| \quad (6)$$

s.t. $T_k(\mathbf{x}) - \mathbf{c}_k = \mathbf{0}$

In order to find 3D tumor position at time t according to Eq. (6), a simple grid search can be performed along the ray line connecting the x-ray source and the estimated tumor position on the imager (a grid resolution of 0.1 mm was used throughout this study). Thus, the original 3D optimization problem becomes a simple 1D problem.

It is worth mentioning that index set S need not be restricted to the set of setup images. It can be the set of all projection images acquired during the entire treatment delivery. In this case, we are applying the 3D localization method in a retrospective setting.

Some technical remarks are appropriate at this point.

1. In the above formulation, we have treated the information obtained from previously acquired images as prior knowledge. This is different from standard Bayesian methods where a prior distribution is fixed before any data collection. Hence, our formulation is more accurately described as an empirical Bayesian approach. On the other hand, instead of being the prior probability distribution defined in Eq. (2), an alternative formulation is to incorporate this information into the likelihood function. In this case, if the prior distribution for the 3D tumor position is assumed to be uniform, exactly the same results will be obtained. Assuming a uniform prior can also be interpreted as the maximum likelihood (ML) approach.
2. Notice that the posterior probability distribution for the 3D tumor position in Eq. (4) is not restricted to any particular

shape (e.g., unimodal or symmetric). It is the best fit to the observed data (i.e., 2D tumor position on the imager) given the underlying probability distribution in Eq. (1) and therefore can have any shape depending on the data.

3. It can be shown that the PDF of 2D tumor position on the imager associated with Eq. (1) is $g'(u) = a \cdot l(u) \cdot \exp[-(|u - c|_2^p / \beta^p)]$, where u is an arbitrary 2D point on the imager, $l(u)$ is the distance from the x-ray focal point to the point u on the imager. When $p = 2$, $g'(u)$ is approximately a 2D Gaussian PDF in the neighborhood of tumor location on the imager. In principle, any form of PDF of 2D tumor position on the imager can be converted to the corresponding 3D PDF and thus be accommodated in our formulation, by a transformation of random variables and reasonable assumption of the probability distribution (e.g., uniform) along the ray line connecting the x-ray focal point and each point on the imager. If the tumor detection process furnishes the probability distribution (e.g., the covariance structure of the 2D positions), this extra information can be easily incorporated into our formulation.
4. Last but not the least, the posterior PDF depends on the hyper-parameter p and hence the MAP estimate will be ultimately affected by this parameter. In the special case of $p \rightarrow 0$, the method is equivalent to finding such a point along the ray that yields the smallest number of nonzero terms inside the summation in Eq. (6). It is worth mentioning that this gives the correct solution in the ideal situation where the tumor follows the exact same trajectory, and the motion trajectory is densely sampled by the setup images. To see why this is true, only a point on the trajectory will yield zero terms inside the summation in Eq. (6) (as long as this point has been sampled from a different gantry angle during setup) and any other point will make all terms inside the summation in Eq. (6) nonzero (except in extreme cases). However, in realistic situations, the optimal p values can be different. Its effects on the 3D localization accuracy will be thoroughly investigated in the following sections.

II.B. Simulation study

In order to evaluate our algorithm for real-time 3D localization, we first simulated realistic 3D tumor motion in two cases: linear motion and elliptic motion. For both motions, the

peak-to-peak motion amplitude is 10, 6, and 20 mm in the AP, LR, and SI directions, respectively. To generate the linear motion, we used three sinusoidal functions with the same phase for all three directions and added independent Gaussian noise to each function. To generate the elliptic motion, we used two sinusoidal functions with the same phase for the AP and LR directions and a third sinusoidal function phase-shifted by 90° for the SI direction and added independent Gaussian noise to each function. The motion period is 4 s for all three sinusoidal functions. The standard deviation for the Gaussian noise is 1 mm in all cases. Figure 1 shows the scatter plot of the simulated tumor motion in patient coordinate system for both motions. We can see that they are quite realistic representations of tumor motions that follow a linear trajectory and those with motion hysteresis. In the second case, it is evident that a 3D Gaussian PDF does not represent the 3D motion accurately.

Given the simulated 3D tumor motion as ground truth, we projected all the 3D points onto the 2D imager in a typical rotational geometry for a LINAC, where the source-to-axis distance is 100 cm, the source-to-imager distance is 150 cm, gantry rotates around $6^\circ/\text{s}$, the total acquisition time is 1 min over one full gantry rotation, and the imager sampling rate is 5 Hz. The setup projections were simulated in a similar fashion. The only difference is that different realizations of the Gaussian noise were used. We then applied the real-time 3D localization method using the 2D projection points as the input and the corresponding 3D locations were estimated according to Eq. (6).

II.C. Phantom experiments

A TrueBeamTM LINAC (Varian Medical Systems, Palo Alto, CA) equipped with an on-board kV imaging system (a 140 kV x-ray tube together with an aSi flat panel) was used in the study. The kV detector has an effective area of detection of approximately $40 \times 30 \text{ cm}^2$. The physical pixel size of the kV detector is about 0.39 mm, corresponding to a detector resolution of 1024×768 . The kV source-to-imager distance was set to be 150 cm.

The Washington University 4D PhantomTM motion stage, which consists of a stage with three independently programmable orthogonal axis and a 1D surrogate stage, was used in

FIG. 1. Scatter plot of the simulated tumor motion (with noise added) in patient coordinate system. Left: linear motion and right: elliptic motion. The 3D motion magnitude is about 23 and 20 mm for the linear motion and elliptic motion, respectively.

FIG. 2. Experimental setup showing the programmable motion stage and the physical phantom used in the study.

this study. The system has been shown to have a mean positional and trial-to-trial error of <0.2 mm,¹⁴ which made it an adequate choice for the study. Two gold cylindrical fiducial markers (1.2 mm in diameter and 5.0 mm in length) were implanted in a tissue equivalent wax and inserted in a cylindrical phantom attached to the motion stage, as shown in Fig. 2. The purpose of using two fiducial markers is to simulate the clinical situation, where usually multiple markers are implanted into the patient. The motion stage was programmed to reproduce the actual 3D tumor trajectories of lung and pancreas patients. Table I shows the average tumor motion magnitude and period for the lung and pancreas cases.

Figure 3 shows a region of interest image of a projection image, which contains the two cylindrical gold fiducial markers. Due to the rigidity of the physical phantom, it was only necessary to track one of the markers in this study, which was done using an efficient marker detection algorithm proposed by Mao *et al.*²²

In order to evaluate the accuracy of our real-time 3D tumor localization method, we first activated the 3D motion phantom and acquired continuous kV images while the gantry rotated around a 360° arc. In this way, we can fully test the localization accuracy of the method from all possible gantry angles by simulating an arc therapy treatment. This was achieved by acquiring a standard full-fan CBCT scan in 1 min, at 100 kVp, 20 mA, and 20 ms (pulse length). Projection images were acquired at around 11 Hz and in total 656 projection images were acquired over a full gantry rotation.

TABLE I. Average tumor motion magnitude and period for the lung and pancreas cases.

Tumor motion	Magnitude (mm)				Period (s)
	AP	SI	LR	3D	
Lung case	2.2	8.1	1.2	8.5	2.9
Pancreas case	1.4	4.8	0.7	5.0	3.2

To initialize the real-time 3D localization method, three relevant clinical scenarios were considered in this study. First, fluoroscopic images of the motion phantom were acquired from both AP and lateral directions for setup purposes. Each fluoroscopic acquisition lasted for 10 s and the frame rate was 25 Hz, leading to a total of 500 setup images. The acquisition settings for fluoroscopic scans were 120 kVp, 20 mA, and 8 ms (pulse length). Second, rotational projection images of the motion phantom were acquired over a full gantry rotation for 1 min to reconstruct volumetric CBCT images for setup purposes. The same settings were used for the simulated arc treatment. Last, the projection

FIG. 3. The region of interest image of a cone beam AP x-ray projection. The two arrows indicate the two implanted fiducial markers in the physical phantom. Marker #1 was used for tracking purposes.

images during the simulated arc treatment are used in a retrospective setting to location 3D tumor position. All three acquisitions (fluoroscopic setup, CBCT setup, and simulated arc treatment) used different and nonoverlapping portions of the tumor motion trajectories. For the CBCT setup, we tested three different acquisitions of a full arc, a half arc (the first), and a one-third arc (the first), corresponding to an acquisition time of 60, 30, 20 s and an OBI gantry rotation of 360°, 180°, 120°, respectively.

II.D. Parameter selection and evaluation criteria

In order to fully investigate the effects of the parameter p on the localization accuracy through both simulation and

phantom studies, we chose eight different values: 2, 1.6, 1.3, 1, 0.5, 0.2, 0.1, and 0.01. For each value of p , we applied the real-time 3D localization method using the 2D projection points as the input and the corresponding 3D locations were estimated according to Eq. (6). The algorithm was evaluated in terms of the 3D localization error. For each projection image, the 3D localization error is defined as:

$$e = \sqrt{(x(1) - \hat{x}(1))^2 + (x(2) - \hat{x}(2))^2 + (x(3) - \hat{x}(3))^2} \quad (7)$$

where $x(1)$, $x(2)$, $x(3)$ are the ground truth tumor location in LR, AP, SI directions, respectively, $\hat{x}(1)$, $\hat{x}(2)$, $\hat{x}(3)$ are the estimated tumor location in LR, AP, and SI directions, respectively.

FIG. 4. 3D localization results for the simulated tumor motion along the LR, AP, and SI directions in patient coordinate systems versus gantry angle: (a) linear motion and (b) elliptic motion. The ground truth tumor motion is shown in solid lines and the estimated motion is shown in stars ($p = 2$) and circles ($p = 0.1$).

For a simulated treatment delivery with multiple projection images, we calculated the average, root mean square (RMS), 95th percentile, 99th percentile, and maximum 3D localization errors over all the projection images acquired during delivery.

III. RESULTS

III.A. Results for the simulation study

Figure 4 shows 3D localization results for the simulated tumor motion along the LR, AP, and SI directions for two values of p : 2 and 0.1. Overall, the estimated 3D motion follows closely the ground truth motion at most times, especially in the SI direction. The RMS 3D localization error is about 1.2 and 2.4 mm for the simulated 3D linear and elliptic motions ($p = 0.1$), respectively. These errors are small compared with the overall 3D motion magnitude of over 20 mm in both cases. However, in the case of elliptic motion, the 3D errors (mainly in the AP and LR directions) exceeded 5 mm for a very small percentage of time. These infrequent large localization errors must be effectively managed during dose delivery. Figure 5 shows the 3D localization error for different p values for both linear motion and elliptic motion. In the case of linear motion, the 3D localization error decreases monotonically for decreasing p and flattens out after p falls below 0.1. In the case of elliptic motion, the average, RMS, and 95th percentile errors follow a similar trend, while the 99th percentile and maximum errors exhibit a minimum (albeit shallow) at $p = 0.5$.

III.B. Results for the phantom experiments

Figure 6 shows 3D localization results using the fluoroscopic setup during the simulated arc therapy for the lung and pancreas cases for two values of p : 2 and 0.1. Overall, the estimated 3D motion follows closely the ground truth motion at most times, especially in the SI direction. The RMS 3D localization error is about 0.65 and 0.40 mm, and the 95th percentile error is about 1.5 and 0.8 mm for the lung and pancreas cases ($p = 0.1$), respectively. These errors are small compared with the overall 3D motion magnitude in both cases. The 3D localization results under other setup scenarios are very similar to those under the fluoroscopic setup.

Figure 7 shows the 3D localization error for different p values using the fluoroscopic setup for both cases. In the pancreas case, the 3D localization error decreases monotonically for decreasing p and flattens out after p falls below 0.1. In the lung case, the average, RMS, and maximum errors follow a similar trend, while the 95th and 99th percentile errors exhibit a minimum (albeit shallow) at intermediate p values (1.6 and 0.5, respectively).

Table II shows the RMS 3D localization error for the lung and pancreas cases, obtained with $p = 2$ and 0.1. The RMS 3D localization error is less than 1 mm in both cases for all three scenarios. The 3D localization error does not change much for different scenarios with the same p value, either with fluoroscopic setup, CBCT setup (including full arc, half arc, and 1/3 arc), or applied retrospectively. These differ-

Fig. 5. 3D localization error versus $-\lg(p)$, where $p = 2, 1.6, 1.3, 1, 0.5, 0.2, 0.1$, and 0.01: (a) linear motion and (b) elliptic motion.

ences of the 3D localization errors for different scenarios are not statistically significant.

Our real-time 3D localization method has been implemented on the MATLAB platform. With a 2.80 GHz CPU and 4GB RAM, the marker detection takes about 32 ms per projection for a typical ROI size of 100×150 . The computational time for 3D localization for each projection depends on the number of projection images acquired in the patient setup process. It takes about 77 ms for the 20-s fluoroscopic setup, 102 ms for the 1-min full-arc CBCT, 58 ms for 30-s half-arc CBCT, 29 ms for 20-s 1/3 arc CBCT, and 102 ms when used retrospectively. Although they are not negligible, it is expected that when implemented on a low-level language such as C, and especially on a multicore platform, these processing times will be reduced dramatically to a negligible level.

FIG. 6. 3D localization results for the simulated tumor motion along the LR, AP, and SI directions in patient coordinate systems versus gantry angle using the fluoroscopic setup: (a) lung case and (b) pancreas case. The ground truth tumor motion is shown in solid lines, and the estimated motion is shown in stars ($p = 2$) and circles ($p = 0.1$).

IV. DISCUSSIONS

We formulated the 3D localization problem from a single x-ray imager in a general Bayesian framework. In contrast to previous top-down approach,²³ we adopted a bottom-up approach. Instead of assuming a simple 3D Gaussian PDF for tumor motion, we constructed motion probability distribution directly from the 2D tumor positions estimated from the projection images. The resultant motion probability distribution is data-dependent and is not restricted to any particular shape. Thus, it gives a more realistic representation of the underlying tumor motion characteristics. One distinct advantage of this work is that there is no model parameter to be optimized, and therefore, it can be easily adopted for routine clinical use.

In this study, we have focused on 3D tumor localization based on continuous kV x-ray images acquired by the on-board imager and with the help of implanted fiducial markers. It can equally be applied to cine MV images acquired by EPID (Ref. 24) and in cases where fiducial markers are not available for tracking purposes (as a result, tracking is relied on soft tissues instead²⁵). However, the relatively large errors associated with either method compared with marker detection in kV images would require the incorporation of this uncertainty into the 3D localization process. Such incorporation would be difficult with the previous formulation.¹⁸ However, it can be easily accommodated by our method, by transforming the uncertainty of 2D tumor position on the imager to the prior and likelihood functions.

FIG. 7. 3D localization error versus $-\lg(p)$, where $p = 2, 1.6, 1.3, 1, 0.5, 0.2, 0.1$, and 0.01 , using the fluoroscopic setup: (a) lung case and (b) pancreas case.

In most cases, our real-time 3D localization method provides reasonable results. The average, RMS, and extreme errors are small compared with the magnitude of the underlying motion. One notable exception is the case of the simulated 3D elliptic motion, where the 95th percentile error is around 5 mm. This happens when the imager is approximately perpendicular to the plane in which the elliptic tumor motion lies. It is important to manage these infrequent large localization errors during treatment delivery. One possible way to improve the current method and reduce these large errors is to incorporate a dynamic model of the underlying motion into the Bayesian formulation. Notice that for the underlying motion, we have assumed a 3D Brownian motion, which is one of the simplest stochastic processes. In reality, there are some patterns and regularities in the tumor motion (especially respiratory motion) that could be effectively captured by a dynamic model, analogous to those built for motion prediction purposes.²⁶ The optimal dynamic motion model would depend on the specific characteristics of the underlying tumor motion. This deserves further investigation and will be the topic of our future study.

A discussion about the effect of p on the performance of the proposed 3D tracking method is appropriate here. In both the simulation and phantom study, it was found that a sufficiently small p (less than 0.1) is optimal in terms of the average and RMS 3D localization errors. Our method with $p = 2$ does provide reasonable tracking results, and the difference in tracking error from the optimal one is small in most cases (except for the simulated linear motion). The reason that the algorithm tends to favor a small p in terms of the average

and RMS error is probably due to our particular problem at hand: the 3D fiducial position in the patient coordinate is not directly measured and only partially observed; what is observed is the projected 2D position on the imager (i.e., incomplete data), which is a complex nonlinear transformation of the variable of interest—the 3D position. This is also related to the validity of using a sufficiently small p in the ideal situation where the tumor follows the exact same trajectory, and the motion trajectory is densely sampled by the setup images, as discussed in the technical remarks. However, when it comes to extreme errors (such as 95th percentile, 99th percentile, and maximum errors), the optimal values of p seem to be case dependent: for the simulated linear motion and pancreas case, a sufficiently small p is optimal; on the other hand, for the simulated elliptic motion and lung case, an intermediate value of p is optimal, although the difference is quite small. This suggests that the motion patterns of different tumors can affect the “optimal” choice of p . On the other hand, the tenability of p enhances the flexibility of the proposed tracking method, allowing the development of heuristics to determine the optimal p value for a given patient.

In clinical practice, one way to select the optimal p value for a particular patient is to apply the proposed method in the retrospective setting using the x-ray images acquired during patient setup. This process can be finished within a few seconds and well before the start of the actual treatment delivery. Once the optimal p value is found, it can be fixed during dose delivery for that treatment fraction. As we have shown in the results, for a fixed p value, the 3D localization

TABLE II. RMS 3D localization error under different scenarios for the lung and pancreas cases.

3D RMS localization error (mm)		Fluoroscopic setup	CBCT setup			Retrospective
			Full arc	Half arc	1/3 arc	
Lung case	$p = 2$	0.76	0.80	0.80	0.80	0.76
	$p = 0.1$	0.65	0.73	0.73	0.73	0.65
Pancreas case	$p = 2$	0.50	0.51	0.51	0.50	0.51
	$p = 0.1$	0.40	0.43	0.44	0.47	0.39

can be done within 0.1 s on MATLAB (this can be further reduced to well below 0.1 s if implemented on a low level language); hence our proposed method can be effectively considered as “real-time” for all practical clinical applications. Whether the optimal p values will change and how much the variation will be among different patients or different treatment fractions is still unknown at this stage. This can be addressed with a retrospective study using multiple patient datasets.

The advantage of computer simulations is that one can separate the errors due to the 3D localization method based on a single imager from those due to marker detection and geometric uncertainties in the on-board imager.²⁷ We repeated the physical phantom experiments using computer simulations for the lung case in the retrospective scenario. Notice that on computers, marker detection and imaging geometry are both perfect. It turned out that the 3D localization error is about 0.18 mm on average (compared with 0.52 mm for phantom experiments) and 0.79 mm at 95th percentile (compared with 1.27 mm for phantom experiments).

V. CONCLUSION

We have developed an algorithm for real-time and full 3D tumor localization with a single x-ray imager during treatment delivery. The 3D localization problem is formulated in a Bayesian framework, where the posterior motion probability distribution is data-dependent and gives a more realistic representation of the tumor motion characteristics. The algorithm was evaluated using a physical phantom with the 3D tumor motion trajectories from real patients. The 3D localization error is <1 mm on average and <1.5 mm at 95th percentile under several clinically relevant scenarios. The proposed algorithm eliminates the need for any population based model parameters in monoscopic image guided RT and is promising for accurate and real-time 3D tumor localization on current standard LINACs with a single x-ray imager.

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