A METHOD TO ESTIMATE MEAN POSITION, MOTION MAGNITUDE, MOTION CORRELATION, AND TRAJECTORY OF A TUMOR FROM CONE-BEAM CT PROJECTIONS FOR IMAGE-GUIDED RADIOTHERAPY

Per Rugaard Poulsen, Ph.D.,*† Byungchul Cho, Ph.D.,* and Paul J. Keall, Ph.D.***

Department of Radiation Oncology, Stanford University, Stanford, CA; and Department of Medical Physics, Department of Oncology, Aarhus University, Denmark

Purpose: To develop a probability-based method for estimating the mean position, motion magnitude, and trajectory of a tumor using cone-beam CT (CBCT) projections.

Method and Materials: CBCT acquisition was simulated for more than 80 hours of patient-measured trajectories for thoracic/abdominal tumors and prostate. The trajectories were divided into 60-second segments for which CBCT was simulated by projecting the tumor position onto a rotating imager. Tumor (surrogate) visibility on all projections was assumed. The mean and standard deviation of the tumor position and motion correlation along the three axes were determined with maximum likelihood estimation based on the projection data, assuming a Gaussian spatial distribution. The unknown position component along the imager axis was approximated by its expectation value, determined by the Gaussian distribution. Transformation of the resulting three-dimensional position to patient coordinates provided the estimated trajectory. Two trajectories were experimentally investigated by CBCT acquisition of a phantom.

Results: The root-mean-square error of the estimated mean position was 0.05 mm. The root-mean-square error of the trajectories was <1 mm in 99.1% of the thorax/abdomen cases and in 99.7% of the prostate cases. The experimental trajectory estimation agreed with the actual phantom trajectory within 0.44 mm in any direction. Clinical applicability was demonstrated by estimating the tumor trajectory for a pancreas cancer case.

Conclusions: A method for estimation of mean position, motion magnitude, and trajectory of a tumor from CBCT projections has been developed. The accuracy was typically much better than 1 mm. The method is applicable to motion-inclusive, respiratory-gated, and tumor-tracking radiotherapy.

Image-guided radiotherapy, Cone-beam CT, Tumor trajectory, Intrafraction motion.
trajectories results in the same sequence of projections. Nevertheless, it is possible to give a good estimate of the 3D trajectory with a probabilistic approach.

In this study, such a probability-based method for tumor trajectory estimation from CBCT projections was developed. The method is investigated for tumors subject to respiratory motion and for prostate both theoretically by CBCT simulations and experimentally by CBCT scanning of a moving phantom. Clinical feasibility of the method is demonstrated for a pancreas cancer case.

**METHODS AND MATERIALS**

Method for estimation of tumor mean position, motion magnitude, and tumor trajectory

This section describes the proposed method for estimation of the mean position, motion magnitude, motion correlation, and trajectory of a tumor from a set of CBCT projections. The next sections describe applications of the method in simulations, experiments, and a clinical case study. The estimation of the tumor trajectory followed two steps: first, the tumor projections were fitted to a 3D Gaussian distribution.

Next, this distribution was used to estimate the tumor trajectory. These steps are explained below. Figure 1 provides a schematic overview of the estimation method and some possible applications.

In the first step, the 3D Gaussian distribution that best fitted the projection data was determined by maximum likelihood estimation (MLE). The Gaussian distribution can be characterized by nine parameters: The mean position \((\mu_{LR}, \mu_{CC}, \mu_{AP})\) in left-right (LR), cranio-caudal (CC), and anterior-posterior (AP) directions, the standard deviations of the position \((\sigma_{LR}, \sigma_{CC}, \sigma_{AP})\) in the three directions, and the correlation coefficients of motion along each direction pair: \(r_{LR-CC}, r_{LR-AP}, \) and \(r_{CC-AP}\). Knowledge of these nine parameters allows calculation of the probability \(P(u,v,\alpha)\) for the tumor to be projected into a point \((u,v)\) on an imager positioned at angle \(\alpha\). The total probability of obtaining the observed combination of projections is given by the product \(P(u,v,\alpha)\) of the probabilities for all projections. In the proposed method, the parameters of the Gaussian distribution are determined by the MLE method, that is, the parameters are selected such that the total probability \(P(u,v,\alpha)\) is maximized (Fig. 2a).

The MLE optimization was implemented in the software package MATLAB (Mathworks, Natick, MA) using a Nelder-Mead simplex search method (7). The optimization starting point for \((\mu_{LR}, \mu_{CC}, \mu_{AP})\) was the mean tumor position as estimated by a least square
The method minimized the sum of the squared distances between the actual tumor projections and the projections that would result from a static tumor. For each CBCT scan, three optimizations with three sets of starting points for \((\sigma_{LR}, \mu_{CC}, \sigma_{AP})\) and \((\rho_{LR,CC}, \rho_{LR,AP}, \rho_{CC,AP})\) were performed and the one resulting in the highest likelihood was selected. Although there is no guarantee that the global likelihood maximum was found by this approach, a more thorough maximum search for selected cases indicated that the resulting Gaussian distributions and the accuracy of the method would not differ substantially with a closer-to-global maximum determination.

For prostate, the LR motion was assumed not to correlate with AP and CC motion, that is, \(\rho_{LR,CC}\) and \(\rho_{LR,AP}\) were approximated by zero instead of being optimized by MLE. This was done because it generally gave better results for prostate, most likely because LR prostate motion usually is small and not well correlated with AP and CC motion (8). For thoracic and abdominal tumors, the generally larger motion ranges and more prominent correlation between LR motion and motion in other directions allowed for inclusion of \(\rho_{LR,CC}\) and \(\rho_{LR,AP}\) in the MLE optimization.

In the second step of the method, the unresolved tumor position was estimated for each projection image by using the 3D Gaussian distribution estimated by MLE in the first step. The details are described elsewhere (9). In short, the tumor is known to be located on the line between the focus point of the imaging system and the projection point \((u,v)\) on the imager. The unknown position along this line is estimated as the expectation value determined by the Gaussian distribution (Fig. 2b). Transformation of the resulting 3D positions from imager coordinates to patient coordinates provided the estimated tumor trajectory.

**Simulation study**

The accuracy of the proposed method was investigated by simulating CBCT acquisition for two large sets of clinical 3D tumor trajectory data. Each trajectory was divided into segments of 60 sec for which CBCT acquisition was simulated.

The simulation for thoracic/abdominal tumors was based on 160 tumor trajectories (46 patients) estimated by a CyberKnife Synchrony system (Accuray, Sunnyvale, CA) at Georgetown University Hospital by using a correlation model between internal tumor motion and motion of external surrogates monitored at 25 Hz (10). The duration of the trajectories ranged from 8 to 110 min, and the total number of 1-min segments for CBCT simulation was 5,113. The mean and maximum motion range for the segments were 2.5 mm and 26.5 mm (LR), 6.8 mm and 56.6 mm (CC), and 3.3 mm and 37.4 mm (AP).

The simulation for prostate was made for 548 trajectories recorded at 10 Hz with implanted electromagnetic transponders (Calypso Medical Technologies, Seattle, WA) for 17 patients treated in supine position at M.D. Anderson Cancer Center Orlando (11). The duration of the trajectories ranged from 3 to 18 min. The total number of 1-min prostate trajectory segments for simulation was 5,323. The mean and maximum motion range for these segments were 0.7 mm and 4.5 mm (LR), 1.5 mm and 17.8 mm (CC), and 1.8 mm and 19.1 mm (AP).

The CBCT simulations were performed by projecting the tumor positions of each trajectory segment onto a flat panel detector that was assumed to rotate 360° clockwise in 60 sec starting with the detector to the right of the patient (and the x-ray source to the left of the patient). An imaging frequency of 10 Hz was assumed, resulting in 600 projections per scan.

The simulated projections were used for estimation of the Gaussian probability distribution with MLE, and the resulting Gaussian parameters were compared with the actual values of \((\mu_{LR}, \mu_{CC}, \mu_{AP}), (\sigma_{LR}, \sigma_{CC}, \sigma_{AP}), (\rho_{LR,CC}, \rho_{LR,AP}, \rho_{CC,AP})\) as directly calculated from the actual 3D trajectory. The trajectories were estimated by use of the Gaussian distribution and compared with the actual trajectories for calculation of the root-mean-square (rms) error and maximum error for each trajectory.

Finally, to investigate potential improvements, \((\mu_{LR}, \mu_{CC}, \mu_{AP}), (\sigma_{LR}, \sigma_{CC}, \sigma_{AP}), (\rho_{LR,CC}, \rho_{LR,AP}, \rho_{CC,AP})\) were recalculated directly from the estimated trajectories and again compared with the values for the actual trajectories.

**Experimental study**

The method was experimentally investigated by acquiring CBCT scans of a phantom on a 3D motion stage (12) that reproduced two selected patient-measured trajectories: a typical lung tumor trajectory and a prostate trajectory with large motion in the axial plane. Before CBCT acquisition, the origin of the motion stage was calibrated such that a 1-mm-diameter spherical marker in the phantom coincided with the CBCT isocenter within 0.5 mm.

The CBCT scans were acquired with an On-Board Imager system mounted on a Trilogy linear accelerator (Varian Medical Systems, Palo Alto, CA). The scan duration was 60 sec during which approximately 640 projections were acquired over 360° with a frame rate of 10.7 Hz. The pixel length in the projection images was 0.388 mm at the detector and 0.259 mm at the isocenter. The projected position of the marker in the phantom was extracted automatically from each image by a research prototype version of the RPM-Fluoro application, version 0.7.10 (Varian Medical Systems). A calibration scan of the static phantom positioned with the marker in the isocenter of the CBCT system was used for correction of offsets and gantry-angle-dependent flex of the imager system. The projected position of the static marker was fitted to a sine function in the CC direction and a constant value in the direction perpendicular to the CC axis, which were then subtracted from the experimentally obtained projections of the moving phantom.

The 3D trajectories were estimated from the extracted marker positions by the proposed method and compared with (1) the actual trajectories used to drive the motion stage and (2) the trajectories when estimated from simulated rather than experimental projections. These simulations were made with the same number of projections, acquisition times, and acquisition angles as in the experiments.

The uncertainties in the experimental study included the accuracy of the motion stage positioning (submillimeter) (12), the accuracy of the marker extraction (approximately 1 pixel = 0.26 mm), and the residual error after correction for imager offsets and flex (subpixel).

**Clinical case study**

In a retrospective study, the CBCT projections for a patient with two markers implanted in the pancreas were used to demonstrate clinical use of the method. As in the experimental investigation, the tumor trajectory was estimated from the extracted position of one marker in the projection images. For comparison with a true 3D measurement, the marker was delineated in each of 10 respiratory phases of a 4D CT scan of the patient by using a segmentation threshold of 2000 HU. The center-of-mass position of the delineated marker was compared with the 3D trajectory estimation from the CBCT projections. The 4D CT scan was acquired the same day as the CBCT scan.
RESULTS

Simulations of CBCT scans

Table 1 summarizes the errors in the Gaussian distribution parameters estimated in the simulations. The table reports the rms and the maximum error for each parameter in the Gaussian distribution for thoracic/abdominal tumors and for prostate. The distribution of estimation errors for the mean position and standard deviation are presented in Figs. 3 and 4. In the LR and AP directions, these distributions were somewhat broader for prostate than for thoracic/abdominal tumors. In the CC direction, both tumor sites showed very small estimation errors.

Fig. 5 shows the estimated motion correlation coefficients for different pairs of directions as function of the actual correlation coefficients. For thoracic/abdominal tumors, all three correlation coefficients were estimated (Figs. 5a–5c), whereas only $\rho_{CC-AP}$ was estimated for prostate (Fig. 5d). The CC-AP prostate motion correlation was predominantly positive meaning that anterior prostate motion was often accompanied by cranial motion.

Table 2 presents key values describing the accuracy of the estimated tumor trajectories in the simulations. The rms and maximum error were calculated for each simulated trajectory. The mean and maximum trajectory rms error and the maximum error in any point along any track are reported in the table. The distribution of 3D rms errors in the trajectory estimations are shown in Fig. 6. The distribution was more narrow for prostate (Fig. 6b) with most 3D rms errors being

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<th>Mean position (mm)</th>
<th>SD (mm)</th>
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<td></td>
<td>LR</td>
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<td>rms error</td>
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<td>Maximum error</td>
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<td>Prostate (17 patients, 548 fractions, 5,323 CBCT simulations)</td>
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<tr>
<td>rms error</td>
<td>0.04</td>
<td>0.0008</td>
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<tr>
<td>Maximum error</td>
<td>0.84</td>
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Abbreviations: 3D = vector; AP = anterior-posterior; CBCT = cone-beam CT; CC = cranio-caudal; LR = left-right; SD = standard deviation of tumor position.

* For prostate, the correlation coefficients between motion in LR direction and the other directions were assumed to be zero and therefore not optimized by the maximum likelihood method.
between 0.05 mm and 0.3 mm. The 3D rms error exceeded 1 mm for 0.9% of the thoracic/abdominal trajectories and 0.3% of the prostate trajectories.

Fig. 7a compares the estimated tumor trajectory with the actual trajectory for a typical thoracic tumor case. The figure presents the rms and maximum estimation errors in each direction. The trajectory with the largest vector rms estimation error (2.89 mm) is compared with the actual trajectory in Fig. 7b. The large estimation error in the LR direction at approximately 40 sec resulted from fluctuating motion correlation during the CBCT acquisition (see Discussion). Figure 8 shows the estimated trajectory for a representative prostate case and a prostate case with large estimation errors.

Recalculation of \((\mu_{LR}, \mu_{CC}, \mu_{AP})\), \((\sigma_{LR}, \sigma_{CC}, \sigma_{AP})\), and \((\rho_{LR-CC}, \rho_{LR-AP}, \rho_{CC-AP})\) directly from the estimated trajectories only improved the accuracy in the CC direction, for which MLE already resulted in very high accuracies, as seen in Table 1. For thoracic/abdominal tumors, the recalculation reduced the maximum error of \(\mu_{CC}\) and \(\sigma_{CC}\) to 0.01 mm and 0.05 mm, respectively. For prostate, the maximum errors were reduced to 0.004 mm \(\left(\mu_{CC}\right)\) and 0.007 mm \(\left(\sigma_{CC}\right)\).

Experimental study

The experimentally investigated trajectories are shown in Figs. 9a and 9b. Each graph compares the actual phantom trajectory with the trajectory estimated both from the extracted marker position in the CBCT projections and from simulated projections. The difference between each trajectory pair can be characterized by its mean value and its standard deviation, which represent a systematic difference and a random difference, respectively. These quantities are presented in Table 3.

In the experimental investigation of the prostate trajectory, the tabletop was unintentionally shifted away from the fine adjusted isocenter position and back again to the same lateral couch readout before CBCT acquisition. Failure to reach exactly the same position probably caused the relatively large systematic difference between experiment and simulation in the LR direction (Fig. 9b).

Clinical case study

Fig. 10 shows an anterior projection from the CBCT projection data set for a pancreas cancer patient. The projected position of the most caudal marker was extracted from each projection and used for estimation of the trajectory shown in the middle panel of Fig. 10. The right side of Fig. 10 shows the marker position in the 4D CT scan with the same vertical scale as used for the CBCT estimated trajectory.

DISCUSSION

The developed method for assessment of tumor motion from CBCT projections lead to very accurate estimations of the mean and standard deviation of the tumor position (Table 1, Figs. 3 and 4). In more than 10,000 CBCT simulations of patient-measured tumor trajectories, no 3D error in the mean position estimation exceeded 1 mm, and no error in any standard deviation component exceeded 1.5 mm. The method also provided good estimations of the tumor trajectories with a mean 3D rms error less than 0.2 mm for both tumor sites. The experimental investigation demonstrated that the high accuracy anticipated by the simulations is not notably degraded in a practical setting by the additional experimental
inaccuracies. It paves the road for clinical application as demonstrated by the clinical case study.

Previously, only a few studies have explored tumor trajectory estimation from CBCT projections. Marchant et al. (13) demonstrated that useful information about the tumor motion can be extracted from the projected position of a marker. By fitting observed marker projections to the expected projections of a static target, the mean position of a cyclically moving phantom was experimentally determined with an accuracy of 1 mm or less (1 SD) in each direction. The motion magnitude in the CC direction was determined from the entire set of projection images, whereas only a subset of projections in angle intervals of ±10° around the vertical and horizontal directions were used for determining the motion magnitude in the LR and AP directions, respectively.

![Fig. 5](image)

**Fig. 5.** Estimated motion correlation coefficient as function of actual correlation coefficient for thoracic/abdominal tumors in (a) LR-CC directions, (b) LR-AP directions, and (c) CC-AP directions, and (d) for prostate in CC-AP directions. CBCT = cone-beam CT; CC = cranio-caudal; LR = left-right; AP = anterior-posterior.

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<th>Table 2. Simulation study: Mean and maximum of the root-mean-square (rms) error of the estimated trajectories, maximum error for all estimated tumor trajectories</th>
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<tr>
<td><strong>LR</strong> (mm)</td>
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**Abbreviations:** 3D = three-dimensional vector; CBCT = cone-beam CT; AP = anterior-posterior; CC = cranio-caudal; LR = left-right.
In the method of the present study, the full 2D information of all projections is readily used in the MLE estimation of the Gaussian probability density. The largest errors were found in the LR and AP directions, that is, in the axial plane where the position component along the imager axis is unresolved and therefore not possible to determine exactly. In contrast, the CC position is resolved for all imaging angles, and the only CC error contribution is magnification errors resulting from inaccurate estimations of the unresolved position. A wrong estimation by 13.6 mm (the largest error in this study; Table 2) leads to an error in the CC position of only 1.4%. Hence, the estimation of the mean position and standard deviation in the CC direction was very accurate (Figs. 3 and 4).

The MLE method in general provided good estimates of the motion correlation (Fig. 5, Table 1). The LR-AP motion correlation of thoracic/abdominal tumors was estimated slightly less accurately than the correlations involving CC motion, which is to be expected because the LR and AP positions are never resolved simultaneously during CBCT acquisition. In general, the motion correlation was considerably larger for thoracic and abdominal tumors (Fig. 5a–5c) than for prostate (Fig. 5d), which was presumably a major reason for the better estimations of mean position and standard deviation for thoracic and abdominal tumors (narrower distributions in the upper row in Figs. 3 and 4).

Most tumor trajectories were well estimated. In 99.1% of the thoracic/abdominal cases and in 99.7% of the prostate cases, the 3D rms error of the estimated trajectory was less than 1 mm. Similar to the mean positions and standard deviations, the trajectories were estimated markedly better in the CC direction than in the axial plane (Table 2).

Figs. 7b and 8b illustrate that even in cases with large trajectory estimation errors, the LR position was estimated correctly around 15 sec and 45 sec, which corresponded to posterior and anterior imaging angles, respectively. Similarly, the AP position was always estimated accurately around 0, 30, and 60 sec (left, right, and left imaging).

In general, the correlation between CC motion and either LR or AP motion will primarily be established from projections in certain gantry-angle intervals (in which the LR/AP motion in question is resolved) and used for trajectory estimation in perpendicular angle intervals (in which the LR/AP motion is unresolved). Therefore, the trajectory estimation method can be vulnerable to fluctuating motion correlations during the CBCT scan.
The trajectory in Fig. 7b illustrates this point. Here, the positive LR around 40 sec was wrongly estimated as negative displacement. The $r_{LR-CC}$ estimation is mainly based on the time intervals around 15 and 45 sec, where both LR and CC motion are resolved. In this particular case, most motion occurred in the second of these intervals (45 sec), where the LR motion was positive and the CC motion was negative. Therefore, $r_{LR-CC}$ was estimated as being negative. When a large positive CC displacement occurred around 40 sec, the unresolved LR displacement was thus estimated wrongly as negative LR displacement. This example illustrates that the trajectory estimation can be less accurate with unstable motion correlation during the CBCT scan.

In comparison with thoracic/abdominal tumors, the mean position errors and standard deviation errors for prostate had broader distributions (Figs. 3 and 4). Furthermore, the motion correlation for prostate was in general weaker (Fig. 5d), and $r_{LR-CC}$ and $r_{LR-AP}$ were not even estimated for prostate. As a result, less accurate trajectory estimations should be expected for prostate, but this is not reflected by the mean and maximum errors (Table 2). A lower accuracy for the prostate trajectory is, however, revealed by the absence of very accurate prostate trajectory estimations with rms errors below 0.05 mm. Such cases constituted only 0.1% of the prostate cases (Fig. 6b) in contrast to nearly 30% for thoracic/abdominal tumors (Fig. 6a). Also apparent from Fig. 6 is a smaller tail toward large errors in the prostate error distribution (most likely because of the generally smaller motion magnitude for prostate), which resulted in mean and maximum errors that were similar to those of thoracic/abdominal tumors (Table 2).

The results of the experimental study are summarized in Fig. 9 and Table 3. The difference between the experimentally derived and actual phantom trajectories includes imperfect phantom alignment with the isocenter. This contribution will show up as a systematic shift (a finite mean error), which was actually the main contributor to the observed difference (Table 3). Except for some systematic shifts, there was close agreement between the trajectories estimated from experimental projections and from simulated projections (Fig. 9, Table 3). It indicates that the errors introduced in the experimental setting will not notably influence the conclusions from the simulation study. The experimental investigation thus serves as a link to clinical applications.
In the clinical case study (Fig. 10), the accuracy of the trajectory estimation is unknown because the actual tumor motion is unknown. However, the good results in the simulations and experimental study indicate that the estimated tumor trajectory is very close to the actual tumor motion. This is supported by the 4D CT scan (Fig. 10, right), which showed similar motion magnitude and motion correlation (positive CC motion correlated with negative LR and AP motion).

The method provides important information for motion-inclusive, respiratory-gated, and tumor-tracking image-guided radiotherapy. With motion-inclusive radiotherapy, in which intrafraction tumor motion is accounted for by margins, an accurate estimation of the mean tumor position is essential for minimizing systematic errors. Because the standard deviation and tumor motion correlation allow calculation of appropriate margins that account for both motion magnitude and directionality (14), these quantities are valuable in evaluating and verifying margins for respiratory motion. They could be used for adaptation of margins or selection of motion management strategy (e.g., motion-inclusive radiotherapy or gating) for individual treatment sessions.

For respiratory gating, the estimated 3D trajectory allows visualization of the gating window to accommodate daily baseline shifts.

For tumor tracking, the presented method for trajectory estimation requires modifications because it is retrospective and requires two parses of all CBCT projections: a first parse for estimating the probability density and a second for estimating the trajectory. In an online implementation (e.g., for tracking during arc treatment), the probability density could be estimated either by a preceding CBCT scan or by use of the subset of projections recorded up to the present point in time.

CONCLUSION

A novel probability-based method for accurate estimation of the mean position, motion magnitude, motion correlation, and trajectory of a tumor from CBCT projections has been developed. Simulations demonstrated the applicability of the method for tumors with periodic respiratory motion and for prostate. Clinical feasibility was demonstrated for a pancreas tumor. Limitations of the method include dependency on implanted markers and reasonably stable motion correlations.
REFERENCES