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Planning four-dimensional intensity-modulated arc therapy for tumor tracking with a multileaf collimator

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Abstract

This study introduces a practical four-dimensional (4D) planning scheme of IMAT using 4D computed tomography (4D CT) for planning tumor tracking with dynamic multileaf beam collimation. We assume that patients can breathe regularly, i.e., the same way as during 4D CT with an unchanged period and amplitude, and that the start of 4D-IMAT delivery can be synchronized with a designated respiratory phase. Each control point of the IMAT-delivery process can be associated with an image set of 4D CT at a specified respiratory phase. Target is contoured at each respiratory phase without a motion-induced margin. A 3D-IMAT plan is first optimized on a reference-phase image set of 4D CT. Then, based on the projections of the planning target volume (PTV) in the beam's eye view (BEV) at different respiratory phases, a 4D-IMAT plan is generated by transforming the segments of the optimized 3D plan by using a direct aperture deformation (DAD) method. Compensation for both translational and deformable tumor motion is accomplished, and the smooth delivery of the transformed plan is ensured by forcing connectivity between adjacent angles (control points). It is envisioned that the resultant plans can be delivered accurately using the dose rate regulated tracking (DRRT) method which handles breathing irregularities (Yi *et al* 2008). This planning process is straightforward and only adds a small step to current clinical 3D planning practice. Our 4D planning scheme was tested on three cases to evaluate dosimetric benefits. The created 4D-IMAT plans showed similar dose distributions as compared with the 3D-IMAT plans on a single static phase, indicating that our method is capable of eliminating the dosimetric effects of breathing induced target motion. Compared to the 3D-IMAT plans with large treatment margins encompassing respiratory motion, our 4D-IMAT plans reduced radiation doses to surrounding normal organs and tissues.

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I. INTRODUCTION

Internal organ motion induced by respiration may result in geometric misses and dosimetric uncertainties in the delivery of intensity modulated radiation therapy (IMRT) (Gierga *et al* 2004, Kissick *et al* 2005, Pehler *et al* 2001, Bortfeld *et al* 2002, Yu *et al* 1998). Such motion-induced dosimetric effects become very complicated when the treatment delivery involves dynamic multileaf movement. The inter-play of target movement and the motion of the radiation field may lead to large errors in the delivered dose (Yu *et al* 1998). To prevent a target miss, an internal margin (IM) around the clinical target volume (CTV) is normally introduced during the treatment planning (ICRU Report 62 1999, Langen and Jones 2001). However, the introduction of an IM inevitably brings unwanted dose to healthy tissues, and increases the possibility of morbidity.

To increase the health-tissue sparing of IMRT treatment when respiratory motion is involved, several margin-reduction techniques have been proposed, such as passive or active breath-holding techniques (Korremann *et al* 2005, Wong *et al* 1999), respiratory gating (Ohara *et al* 1989), tumor tracking and compensating (Yi *et al* 2008, Schweikard *et al* 2004, D'Souza *et al* 2005, Depuydt *et al* 2011, Keall *et al* 2001), etc. In breath-holding techniques, the radiation beam is turned on while the treatment area is made still by a voluntary or forced breath hold. This causes discomfort to patients and increases treatment time. Respiratory gating, which relies on the ability to turn the radiation on only during the desired portion of breathing cycles, has been widely adopted for the delivery of fixed-gantry IMRT (Kubo *et al* 1996). However, treatment efficiency inevitably decreases due to the inherent duty cycle of gating techniques. Tumor tracking is a technique that dynamically repositions and reshapes the radiation beam to track tumor movement. Keall *et al* first introduced a tracking method that dynamically controls the leaf positions of the MLC to synchronize with target motion under real-time monitoring. Under ideal conditions, MLC tracking can be performed with 100% accuracy, and the delivery will not be prolonged nor interrupted. For fixed-field IMRT, it has long been established that tumor tracking with an MLC provides promising solutions (Sawant *et al* 2008, McQuaid *et al* 2006, McQuaid *et al* 2009). Yi *et al* proposed another MLC tracking strategy, called dose-rate regulated tracking (DRRT) (Yi *et al* 2008). Unlike the approach of Keall *et al*, the delivery of DRRT starts with a preprogrammed MLC tracking sequence based on regular periodic respiratory motion. Then, by changing the dose rate dynamically, the delivery can be sped up or slowed down to compensate for breathing irregularities at the time of treatment delivery. Because dose-rate variation is supported by modern linear accelerators, the DRRT scheme can be implemented with existing technology.

Intensity modulated arc therapy (IMAT) was first proposed by Yu in 1995 as a treatment delivery using multiple superimposed arcs with varying field shapes (Yu 1995). The technique was further developed for a single arc with aperture-based algorithms for planning optimization (Otto 2008, Bzdusek *et al* 2009). In comparison to fixed-field IMRT, IMAT provides a more efficient approach to deliver similar conformal doses to targets as fixed-field IMRT. Recently, the feasibility of tumor tracking in IMAT delivery is also gaining interest. Davies *et al* have demonstrated the accuracy and efficiency of tumor tracking in IMAT delivery using a commercial MLC (Davies *et al* 2011, Davies *et al* 2013). Considering

tracking latency, the effectiveness of MLC tracking for IMAT was also experimentally validated (Bedford *et al* 2015). Zimmerman *et al*, by integrating the MLC tracking system with an external optical system, demonstrated the possibility of delivering satisfying dose distributions of IMAT plans for lung patients (Zimmerman *et al* 2009, Falk *et al* 2010). For treating prostate patients, X-ray imaging or electromagnetic transponders were also tentatively used for MLC tracking with IMAT delivery (Poulsen *et al* 2010, Keall *et al* 2014).

Besides a reliable technique to compensate for intrafractional motion during IMAT delivery, an effective treatment planning method is also important and necessary. Ma *et al* extended a four-dimensional (4D) IMRT scheme proposed by Trofimov *et al* to rotational delivery based on a periodic pattern of rigid tumor motion in the superior-inferior direction (Trofimov *et al* 2005, Ma *et al* 2010). In their study, motion of the target volume was followed by time (phase) dependent beam portals. An in-house planning system was specially designed using a simulated annealing search engine. To calculate the 4D dose when optimizing the 4D-IMAT plan, they used deformable registration to track the movement of each voxel. The pattern of rigid motion simplified the registration matrix, and therefore the 4D-dose calculation. Another approach was proposed by Chin *et al*, which extended the Otto's algorithm for 3D-IMAT to be used for 4D-IMAT planning (Otto 2008, Chin *et al* 2011). In their 4D algorithm, time-correlated beam samples were progressively added during optimization throughout the full range of a single arc. They investigated the performance of their algorithm by using virtual phantoms with different modes of rigid motion, and later tested the method by incorporating patient data of 4D computed tomography (4D CT) into the planning for lung cases for stereotactic body radiation therapy (SBRT) (Chin *et al* 2013). However, in their study, 4D CT was only used for finding the target center at various breathing phases, and motion of the tumor was regarded as the displacement of target center, while deformation being not considered. Above all, these studies either ignored target deformation, or needed considerable computational capacity.

In this paper, we report on a practical 4D planning scheme of IMAT using 4D CT for tumor tracking. In our 4D-IMAT planning method, no significant extra computational power is required. A 4D-IMAT plan is generated by transforming the segments of a 3D plan optimized on a reference-phase image set of 4D CT. A direct aperture deformation (DAD) method is used for segment transformation. The DAD method, in which both rigid and deformable organ motions are considered, was originally created to compensate for interfractional variations for online replanning (Feng *et al* 2006, Ahunbay *et al* 2008), and was later successfully used for 4D planning of fixed-field IMRT (Gui *et al* 2010, Yang *et al* 2012).

II. METHODS AND MATERIALS

In our planning scheme, realistic requirements for delivery are given as described in Section **II. A**. The proposed method consists of two major components: 1) implementing a practical planning method of 4D IMAT for tumor tracking (**II. B**), and 2) providing a procedure of 4D dose calculation and accumulation for IMAT (**II. C**). To evaluate the performance of our 4D-IMAT planning method, three cases are studied by comparing different planning schemes (**II. D**).

II. A. Scenario of 4D-IMAT delivery

In most commercial implementations of IMAT, the delivery process is presented as a stream of consecutive control points. A control point defines an instantaneous configuration of the MLC leaves at a specific gantry angle, as well as the number of MUs delivered with a planned dose rate between two adjacent designated gantry angles. For the convenience of simulation, the dynamic nature of delivery defined by the control points is approximated by a series of static segments. For 3D-IMAT without considering breathing motion, a segment of a plan has three attributes: aperture shape, MU and gantry angle.

In planning for 4D-IMAT, we assume that patients can breathe regularly with an unchanged breathing period. In addition, regular respiratory motion can be predicted as periodic 3D anatomical changes, which are presented by a set of phase-sorted 4D CT. During the delivery of 4D-IMAT, the irregularities of breathing can be handled, for example, by using the DRRT technique (Yi *et al* 2008). For a patient with regular breathing, we also assume that the start of delivery can be synchronized with a designated respiratory phase and that the execution time of each control point can be predetermined. Under these conditions, an arbitrary segment (control point) of the plan can be associated with a specific respiratory phase and the corresponding image set of 4D CT. In other words, other than aperture shape, MU and gantry angle, in our scenario, the associated respiratory phase becomes a new attribute of the segments.

II. B. 4D-IMAT planning method

Our planning method can be described in three steps, a) initialization, b) transformation and c) connection.

(a) Initiating a 3D-IMAT plan on phase 0—4D CT data sets are acquired on a CT scanner in helical mode (Philips Medical System, Cleveland, OH) with a respiration monitoring device (RPM, Varian Medical System, Inc., Palo Alto, CA). The respiratory cycle is divided into ten phases. For each phase, a gross tumor volume (GTV) is delineated on the image set of 4D CT acquired at that phase, and a planned target volume (PTV) at that phase is obtained by adding a margin from the GTV to account for setup errors (i.e., no IM encompassing intrafractional motion). A 3D-IMAT plan is then optimized to meet the clinical criteria based on the delineation of regions of interest (ROIs) at phase 0.

In this study, we use the SmartArc module of the Pinnacle treatment planning system for IMAT optimization. A total of 177 segments are allowed for a single-arc plan. Therefore, the 3D-IMAT plan is represented by a set of 177 segments:

$$\Phi^{3D} = \{S_n(\theta_0) : n=0, 1, 2, \dots, 176\} \quad (1)$$

where each segment S_n is optimized at phase 0 (i.e., θ_0). In the SmartArc of Pinnacle system, an adaptive version of the collapsed cone convolution algorithm is used for dose calculation.

(b) Transforming the segments of 3D-IMAT plan—In SmartArc, the dose rate and gantry speed for each control point of the 3D-IMAT plan are calculated when the plan is generated. Therefore, the execution time of each segment for the initialized 3D plan can be easily obtained. The total delivery time of a single-arc plan optimized in SmartArc is normally within 60–90 s. Assuming that the gantry rotates with a constant speed and the breathing period of the patient is 4 s, the gantry sweeps 16–24° for each breathing cycle. If the angle spacing of neighboring segments is taken as 2°, then 8–12 control points are executed during each breathing cycle.

Figure 1 shows an example of the delivery schedule and segment-phase association for the initialized 3D plan based on the scenario discussed in Section II. A. Each segment is associated with a specific phase. All the segments associated with phase 0 (e.g., $S_0, S_{10} \dots$ in Fig. 1) have been optimized based on PTV delineation at phase 0. Therefore, they are still regarded as appropriate for the moving target. All other segments need to be transformed to be appropriate for the moving target according to their associated phases.

The DAD method is adopted for modifying each segment according to geometric variation of the target (PTV) in an associated phase with respect to that in phase 0. For a segment associated with phase i , we express it as the following,

$$S_n(\theta_i) = T_{\theta_0 \rightarrow \theta_i} S_n(\theta_0) \quad (2)$$

where $T_{\theta_0 \rightarrow \theta_i}$ is a operator for changing the aperture shape of S_n from phase 0 to phase i . The MU of S_n is not changed.

For implementing the DAD method, Feng *et al* used deformable registration to obtain a 3D transformation-vector matrix that determines the 3D phase-to-phase dislocation of each target voxel (Feng *et al* 2006). Afterwards, 3D vectors of dislocation were projected and averaged to be 2D vectors in the beam's eye view (BEV) (i.e., $T_{\theta_0 \rightarrow \theta_i}$ in Eq. (2)) for aperture-shape modifications. In this paper, we use a segment aperture morphing (SAM) algorithm to obtain the operator $T_{\theta_0 \rightarrow \theta_i}$. The SAM algorithm directly modifies aperture shapes based on 2D anatomical changes as seen from the BEV, avoiding the computational burden of deformable registration in obtaining a 3D matrix.

As described by Anunbay *et al*, the SAM algorithm compares the location and extension of enveloping shapes of old and new target projections in BEV. For each boundary point determining the MLC aperture shape in the old projection, a unique counterpart is calculated in the new projection. In this work, we followed the similar approach as presented by Gui *et al*. The implementation for SAM consists of two steps (i.e., translation and deformation). 1) First, we establish coordinates respectively on phase 0 and phase i for the PTV projections on BEV. Both origins of coordinates are defined according to the contour edges of PTV projections. The origin shift of coordinate from phase 0 to phase i is regarded as the projected PTV translation. A new aperture for phase i is located by shifting the original aperture by the direction and distance of the projected PTV translation. 2) After translation, the deformation of PTV-projection boundary is easily established by making one-to-one

movement mapping for each boundary point from phase 0 to phase i . The movements of all points within the projection boundaries are obtained by linearly interpolating the movement mappings between boundary points. Thus, each boundary point of the phase-0 segment aperture, which is within the phase-0 PTV projection, has a mapped point within the phase- i PTV projection. Then, the MLC-leaf positions of the new aperture for phase i are easily determined by those mapped points in the PTV projection of phase i .

After transforming segments from phase to phase based on the geometric translation and deformation of the PTV in the BEV, we obtain a new 4D-IMAT plan as the following:

$$\Phi^{4D} = \{ \{ S_n(\theta_i) \} : n=0, 1, 2, \dots, 176 \} \quad (3)$$

Here, each segment S_n corresponds to a specified single phase i ($i = 0, 1, 2, \dots, 8, 9$).

(c) Enforcing connectivity between neighboring segments—To insure connectivity, i.e. that the proposed MLC-leaf positions and motions for neighboring segments will obey any physical constraints imposed by the operation of the MLC leaves, we must check and perhaps modify the transformed segments in the set shown in Eq.(3). Leaf speed limitations can be handled if we elongate the delivery times of segments. However, the phase schedule (e.g., see Fig. 1) of control-point execution will then be disrupted. Therefore, to keep the original phase schedule unchanged while achieving deliverability, we truncate the over-limit travels of MLC leaves between each pair of neighboring segments.

In this study, we use a Varian MLC which allows leaf interdigitation. Therefore, the motion of each MLC leaf is not confined by the motion of its adjacent leaves. Thus, travel truncating for each leaf can be done independently.

For a single MLC leaf, the deliverability of time-dependent positions can be realized by forcing connectivity of leaf positions for each breathing cycle. Figure 2 shows how connectivity of leaf positions is enforced during a single breathing cycle. In this example, 10 control points are executed from t_0 to t_{10} . At phase 0 (i.e., t_0 and t_{10}), the leaf positions of the 4D plan are the same as that of the 3D plan before segment transformation. If we keep the MLC leaf positions at t_0 and t_{10} unchanged when repositioning the leaves for other control points between them, a connected solution from t_0 to t_1 is guaranteed, because there exists at least one possibility (i.e., the original trajectory of the 3D plan).

From the 2nd to the 9th control point within the breathing cycle, the two following operations are successively conducted to enforce connectivity of each control point in a downstream-labeled order (i.e., $j = 2, 3, \dots, 9$):

$$(1)x_j^* = \begin{cases} x_j^U, & |x_j^U - x_{j-1}| \leq v_{max}(t_j - t_{j-1}) \\ x_{j-1} + \frac{(x_j^U - x_{j-1})}{|x_j^U - x_{j-1}|} v_{max}(t_j - t_{j-1}), & |x_j^U - x_{j-1}| > v_{max}(t_j - t_{j-1}) \end{cases} \quad (4)$$

$$(2)x_j = \begin{cases} x_{10} + v_{max} (t_{10} - t_j), & x_j^* - x_{10} > v_{max} (t_{10} - t_j) \\ x_j^*, & |x_j^* - x_{10}| \leq v_{max} (t_{10} - t_j) \\ x_{10} - v_{max} (t_{10} - t_j), & x_j^* - x_{10} < -v_{max} (t_{10} - t_j) \end{cases} \quad (5)$$

where x_j^U is the value of x_j before connectivity enforcing, v_{max} is the maximum average leaf speed between two neighboring control points. In this study, the maximum speed, v_{max} , of the MLC leaves is 2.5 cm/s, which is normally used for the constraints of IMAT optimization (Bzdusek *et al* 2009).

By conducting the first operation (Eq. (4)) above for a leaf of one control point, the leaf is tentatively moved from the finalized position of an upstream control point to a position (i.e., x_j^*) approaching the intended position as far as possible within the physically achievable maximum. The second operation (Eq. (5)) ensures that the leaf with a new position can still move to the prefixed downstream position at phase 0 (i.e., x_{10}) within the remaining time (i.e., $t_{10} - t_j$) of the breathing cycle. Such connectivity enforcement is executed for all breathing cycles and for each individual MLC leaf. Opposing leaves need to be double checked for positioning after enforcing connectivity. Finally, the 4D-IMAT plan is imported back to the treatment planning system, where deliverability can be checked again and approved.

II. C. 4D dose calculation and accumulation

The dose distribution of 4D-IMAT cannot be calculated using CT images acquired at a single phase. To evaluate the 4D-IMAT plan, the cumulative dose of the 4D plan is calculated in a 10-phase 4D CT based on the delivery scenario described in Section II. A. For an arbitrary 4D-IMAT plan (i.e., Eq. (3)), the 4D dose can be calculated as the following,

$$D(\Phi^{4D}) = \sum_n R_{\theta_i \rightarrow \theta_0} D[S_n(\theta_i)], i=0, 1, 2, \dots, 8, 9 \quad (6)$$

First, the dose of each segment associated with a specific phase (i.e., $D[S_n(\theta_i)]$) are calculated on the corresponding CT images of that phase. Then, the dose distribution of each segment is geometrically transformed to register with phase 0 (i.e., $R_{\theta_i \rightarrow \theta_0} D[S_n(\theta_i)]$). Finally, the dose distributions of all segments are superimposed onto the CT images of phase 0 as the total 4D dose. Here, $R_{\theta_i \rightarrow \theta_0}$ is a resultant operator from the deformable registration between CT images of phase i and phase 0. If the dose $D[S_n(\theta_i)]$ is presented as voxel doses in 3D, the $R_{\theta_i \rightarrow \theta_0}$ provides the mapping of each voxel from the original position to the new one. In this study, the dose transformations are performed using a commercial image registration system (MIMvista 5.1, MIMvista Corp, Cleveland, OH).

II. D. Testing the 4D-IMAT planning scheme

II. D.1. Planning schemes used for comparison—Three different planning schemes are tested and compared:

(a) 3D plan without IM delivered to a static target. Defining the PTV on phase 0 (e.g. the end of inhalation) of 4D CT without IM, we optimize a 3D-IMAT plan as if the patient was static, and calculate the dose at phase 0. This scheme is taken as a “gold standard” for comparison to other schemes.

(b) 4D plan without IM delivered to a moving target. Starting from the 3D-IMAT plan prepared in scheme (a), we generate a 4D plan using our 4D planning method, and calculate the 4D dose based on the method as described in II. C. The 4D plans, which perform tumor tracking, are expected to show improvements in plan quality compared to the situations without segment transformation. The dosimetric performance comparison of the 4D plans and the “gold standard” 3D plans will reveal the ability of our 4D IMAT planning scheme in eliminating the dosimetric effects of breathing induced target motion.

(c) 3D plan with IM delivered to a moving target. A 3D-IMAT plan is optimized on phase 0 with a PTV defined as the union of the PTVs at all phases of 4D CT. Assuming that the 3D plan is delivered to the moving target with regular breathing, we calculate the 4D dose based on a phase-scheduled delivery. By comparing the resultant plans to that of schemes (b) and (c), the benefits from 4D planning over the margin-enlarging planning technique can be evaluated.

II. D.2. Case study—Three cases are studied by comparing the different planning schemes described above:

(1) A simulated lung case: Figure 3 shows a case that uses a 4D CT data set of a lung patient whose tumor is located near the diaphragm. For our simulation, the original tumor is digitally replaced by a spherical fake tumor of 3 cm in diameter. A translational motion is applied to the tumor with peak-to-peak distances of 1.5 and 0.5 cm in superior-inferior and anterior-posterior directions, respectively. The spherical tumor at phase 0 is considered as a stack of disks, each located on a CT slice. These disks are moved horizontally relative to phase 0 locations according to cosine functions of amplitudes equal to 2/5 of the disk's diameter from the edge and a period identical to that of the patient's breathing cycle. The PTV is obtained by adding a 5 mm margin from the fake-tumor border. The total volume of the PTV is unchanged during breathing. The transformation vectors, which are needed to transform the dose distributions of all phases to register on phase 0, are predetermined. Therefore, 4D dose can be accumulated without using the deformable registration tool. Compared to real patient cases, the simulated case excludes the errors caused by target delineation and deformable registration for 4D dose accumulation.

(2) A Lung patient: A patient has a tumor located at the right middle lobe of the lung. The peak-to-peak distance of PTV-centroid translation during a breathing cycle is around 1.7 cm. The average PTV volume of 10 phases is 26.3 cm³ with 2.7% deviation.

(3) A pancreas patient: For this pancreas case, the peak-to-peak distance of PTV-centroid translation during a breathing cycle is around 1.0 *cm*. The average PTV volume is 75.0 *cm*³ with 7.4% deviation during a breathing cycle.

For both lung and pancreas patients, GTVs are contoured manually by a radiation oncologist on the ten 3D-image sets contained in the 4D CT. The total prescribed doses are 66.6 Gy (i.e., 37 fractions) for the lung cases and 50.4 Gy (i.e., 28 fractions) for the pancreas case, respectively. Although the PTVs are defined differently for the “gold standard” 3D plan of a static patient and the 3D plan with an enlarged margin, they are specified with the same planning goal (i.e., 180 cGy per fraction to the PTV) for all studied cases during plan optimization by using the SmartArc module. For both 3D plans (i.e., PTV with or without IM), the calculated doses on phase 0 are properly normalized so that each PTV coverage is satisfied, i.e., 100% isodose line encircles the majority of the PTV (or PTV union).

Note that the target motion perpendicular to the leaf travel direction may result in large requested leaf shifts between adjacent control points. In this study, for all three cases, we set the MLC at 45° angles to the major axis (i.e., the superior-inferior axis) of tumor motion when initiating the 3D-IMAT plans.

III. RESULTS

III. A. The performance of DAD method

Figure 4 shows two fragments of a single-arc 4D-IMAT plan for the simulated lung case. Connectivity between neighboring segments has been forced. As shown in both series (upper and lower) of Fig. 4, the target is tracked from the end of inhalation to the end of exhalation. By using DAD, the apertures have been shifted and deformed based on the changes of target BEVs (e.g., the lower series in Fig. 4), while the function of modulation is maintained (e.g., the upper series in Fig. 4).

Figure 5 shows the isodose distributions before and after DAD for individual phases. For each phase, the dose distributions of all associated segments are calculated and accumulated. It is clearly demonstrated that, for each phase, the distribution of absorbed dose is rectified to be conformal to the target.

Figure 6 compares the dose of 3D plan on static patient and the 4D cumulative doses of plans (i.e., before and after DAD) on dynamic patient. Target miss due to not considering tumor motion in planning is clearly demonstrated by the comparing (i) and (ii) of Fig. 6 in PTV coverage. Comparing Fig. 6(ii) and (iii), we easily find an improvement of PTV coverage after DAD. Similarly with the “gold standard” plan, the 95% isodose line of the 4D plan conforms tightly around the PTV.

III. B. Connectivity enforcement

Figure 7 compares the leaf trajectories of the 4D plans with and without forcing leaf connectivity for the lung patient. Fig. 7(a) presents a leaf involved with both the “gold standard” 3D plan and the 4D plans. After DAD, the leaf trajectories do not violate the speed limit so that the intended positions of the leaves are connected naturally. Fig. 7(b) and (c)

show the trajectory and speed of a leaf only involved with the 4D plans (i.e., the pair of leaves is closed in original 3D plan). The insignificant difference of leaf positions can be seen before and after forcing connectivity.

Comparing the 4D plans before and after connectivity enforcement, it is found that the values of major plan-quality indicators varied insignificantly (see Table 1).

III. C. Dosimetric performance of 4D-IMAT plans

Figure 8 compares the dose-volume histograms (DVHs) of the 4D plans and the 3D plans with IM for all studied cases. The DVHs of “gold standard” 3D plans are also plotted for comparison.

In principle, as a fair comparison, we refrain from renormalizing a 4D dose distribution of the margin-enlarged 3D plan, because its MUs should have met the original planning goal which was set for the PTV union of all phases. However, here, we slightly adjusted (i.e., less than 2%) the total MUs of 3D plans with IM, so that they have the same D_{50} of the PTV with the “gold standard” 3D plans at phase 0. Then, convenient comparisons with 4D dose could be made between different schemes and different cases in target coverage and OAR sparing. Such MU adjustment, which was based on 4D dose calculation, were applied for all three cases, and it did not affect the original planning goal regarding the 3D dose of PTV union.

In addition to the DVH comparison, the difference in target coverage using different schemes can also be seen in Fig. 9. The “target-miss 3D plans” in Fig. 9 correspond to the 3D plans without IM delivered to a moving target, which are compared to other plans to show the amount of plan-quality degradation due to motion when not considering the motion during planning. It is evident that, in the simulated lung case, the PTV coverage of the 4D plan is comparable to the “gold standard” 3D plan. In the lung patient case, the difference of PTV coverage between the 4D plan and the “gold standard” plan is small (i.e., <1% in V_{95} for PTV). In the pancreas case, the difference of V_{95} for the PTV is approximately 5% between the 4D plan and the static plan.

Figure 10 shows a comparison of the isodose lines for the 4D plan with the 3D plan with IM for the lung and pancreas patients. Similarly with the “gold standard” plans, the 4D plans result in the isodose lines tightly circumscribed around the PTV. The dose distribution is more conformal than the resultant dose distribution of the 3D plans with IM.

In Table 2, we list the dosimetric data for the OARs of all case studies with the three different planning schemes. By observing multiple plan-quality indicators for OARs, we find that the 4D plans, to varying degrees, are generally better in OAR sparing than the 3D plans with MIM. The exceptions are the D_{mean} of the liver of pancreas patient and the D_{mean} of the heart of simulated lung case. In general, for each of the cases studied, the differences of in plan-quality indicators between the 4D plan and the 3D “gold standard” plan are small, and such differences are much less than those between the 4D plan and the 3D plan with MIM. In some cases, the 4D plans perform better than the “gold standard” plans in sparing some OARs (e.g., D_{mean} to the liver of simulated lung).

IV. DISCUSSION

IV. A. The performance of DAD method

In this study, the DAD method, which can account for both translational and deformable tumor motion, was used to transform the radiation therapy plans from 3D to 4D. The ability to compensate for dose variation in PTV coverage by using deformed apertures was demonstrated in the three cases studied. For each case, the resultant 4D plan produced a cumulative dose in the reference phase with good PTV conformity, approaching that of the 3D plan for a static target. For the simulated lung case, we cannot find a significant difference of PTV coverage between the 4D plan and the original 3D plan. For the lung and pancreas patients, the PTV coverage of the 4D plan slightly degrades with respect to the original 3D plan (e.g., V_{95} in Fig. 9). However, the degradation is small, and should be within the clinical tolerance (e.g., 5% deviation from original values).

Many factors may cause PTV-coverage degradation (e.g. in Fig. 9) of the 4D plan with respect to the original 3D plan. Firstly, it might be contributed from inevitable human errors in delineating, i.e., the target deformation is described by manually contoured GTVs on the images of 4D CT. Even if we were aided by a segmentation tool to make the delineation errors as small as possible, we would not have avoided the inaccuracy caused by CT imaging techniques, especially for the cases involved with soft-tissue contrast. Secondly, uncertainties also exist in the process of plan evaluation. In our study, the plan is evaluated based on the 4D dose registered and accumulated on the reference phase. The accuracy of 4D dose relies on the performance of deformable registration routine and the quality of 4D CT. The above two aspects of uncertainties are not unique for our study, and they are of concern for most 4D planning schemes. Another possible uncertainty, which is unique for our study, is due to the DAD method (or the SAM algorithm), if it is deficient in compensating for a very complex tumor deformation. Our simulated lung case was fabricated to exclude the errors caused by target delineation and deformable registration for the 4D dose accumulation. In this case, the tumor is artificially designed, and the rigid motion and deformation (i.e., shifting disks) is predetermined while the PTV size is maintained during the breathing cycle. As seen in Fig. 9, insignificant PTV-coverage degradation in the simulated lung case indicates that, when excluding the possible errors caused by the delineating and 4D dose accumulation, the SAM algorithm performs very well in compensating for such fabricated rigid and deformable motion (i.e., no tumor shrinking/expanding). The lung and pancreas patients should present more complex motion patterns. However, for these cases, it is not easy to exclude the errors of delineation and 4D CT, so as to conclude the performance of SAM. Several attempts to quantify the uncertainty of deformable registration have been reported (Samavati *et al* 2016). Here, an analysis was conducted for the dose error caused by the deformable registration in the environment of our 4D dose accumulation (using MIMvista system). We registered the calculated dose of an initiated plan (e.g. the “gold standard” 3D plan) at phase 0 to the adjacent phase (i.e., phase 1), then sequentially registered the dose between neighboring phases throughout all rest of phases, finally registered the dose of phase 9 back to phase 0. After such “looping registration”, PTV-coverage degradation of registered dose (i.e., at phase 0) was found, regarding 1~1.5% decrease in V_{95} compared to that of the dose initially calculated at phase

0. Although such “looping registration” study may not be able to fully reveal the errors of 4D-dose accumulation for all cases, it implies the amount of error contribution due to the 4D dose accumulation in 4D planning evaluation.

Assuming the accuracy of accumulated 4D dose (i.e., image deformable registration could truly present the nature of breathing), we can slightly adjust MUs to reach specific clinical requirements if needed. For example, in both pancreas and lung patient cases, we find a small amount of missing dose for the PTV compared with the original 3D plan, which can be seen in Figs. 8 and 9. Such insufficiency can be easily repaired by slightly raising the total MU. In Fig. 9, for the lung and pancreas patient cases, if the total MU of the 4D plan is increased by 2%, D_{95} of PTV will be equal to that of original 3D plan. Such MU changes, which will not increase the OAR doses significantly, can be realized by raising the dose rate of delivery while not changing the delivery time and schedule.

Because OARs are not considered in the DAD method, we do not expect an improvement of OAR sparing for the resultant 4D plans with respect to the original 3D plan. However, in this study, we did not see a significant increase of OAR dose due to DAD. In fact, for a specific OAR, a dosimetric change due to DAD depends strongly on the relative position of that OAR to the PTV. Considering the liver of the pancreas patient case, the original 3D plan was optimized at the end of inhalation phase, during which the PTV is at its furthest location relative to the liver. Consequently, when the apertures of the 3D plan were morphed to track the PTV for other breathing phases, the beam inevitably gave a higher dose to the liver because their relative distance decreased. In contrast, the liver dose decreased after DAD in the simulated lung case, because the beam is supposed to move away from liver after the end of inhalation, where the 3D plan was initialized. Such evidence tells us that if the relative distance of the PTV and OAR is considered when the apertures are morphed, OAR sparing may be improved. By using rigidly moving phantoms, Chin *et al* has studied and demonstrated the importance of considering the relative distance of PTV and OAR in 4D planning (Chin *et al* 2011). However, similar study has not been conducted for real patients with 4D CT, therefore, should be pending for the future.

Our results indicate that a 4D-IMAT plan, which is produced by geometrically modifying a 3D plan optimized for the reference phase, is almost as good as the original 3D plan on a static target. Although we only tested on a limited number of cases, we expect that this conclusion will hold true for most cases where the target is subject to respiratory-induced motion. Our study, as a continuation of the previous works (Yang *et al* 2012, Gui *et al* 2010) describing 4D planning for fixed-field IMRT, demonstrates the efficacy of the DAD method in 4D planning, and verifies the feasibility of this method in 4D-IMAT planning.

IV. B. Effects of connectivity enforcement

Sun *et al* developed a dynamic MLC tracking algorithm to compensate for two-dimensional (2D) target motion in the BEV for IMAT delivery (Sun *et al* 2010). In their work, an IMAT plan was also initiated at one particular phase of the breathing cycle without IM. When tumor tracking was engaged, in order to maintain tracking accuracy of each MLC leaf, they decreased the gantry rotating speed, resulting in an increase in the delivery time as compared to the delivery without tumor tracking. Unlike their study, we maintain the original gantry

speed, and also guarantee the delivery of tracking by forcing connectivity between neighboring control points. Therefore, some degradation of plan quality may be expected due to such enforcement. However, for the cases we studied, connectivity enforcement did not cause much difference between the deliverable versus intended trajectories (e.g., Fig. 7), and consequently, did not significantly compromise plan quality.

One factor that may affect the degree of difficulty for connectivity enforcement is the initial angle of the collimator. By minimizing the geometrical change of the target in the BEV during breathing in the direction perpendicular to MLC travel, we can ease the busy movement of MLC leaves when tracking the tumor. In this study, we always set the MLC to 45°, and did not seek the optimal collimator angles for ease of tracking.

Another factor affecting connectivity is that the desired MLC-leaf motions were moderate in the initial 3D-IMAT plan. Because the target motion is continuous and gradual, any additional desired MLC-leaf motion for tracking the tumor is also moderate. As a result, the number of leaf positions required to be altered relative to the number of leaves positions involved in field shaping is relatively small and the position adjustments required to achieve connectivity are also small. In this study, all 3D plans were optimized by using the Pinnacle system in which direct aperture optimization was used. Plans that are optimized in Pinnacle normally consist of moderately modulated apertures, while maintaining a high plan quality. Naturally, compared to highly modulated apertures, these apertures are more easily connected after morphing. In this study, we did not deliberately produce highly modulated 4D plans. Actually, at least in our studied thoracic and abdominal cases, we did not see the necessity of highly modulated plans in achieving goals regarding clinical specifications. Therefore, the relation of plan-quality degradation due to connectivity enforcement and the degree of modulation needs further study.

Using connectivity enforcement, the delivery efficiency of the plans for tracking is ensured to be the same with that of the plans without tracking. Therefore, if plan-quality degradation is negligible, forcing connectivity during planning is advantageous rather than a post-planning strategy of slowing down gantry rotation when considering tracking issues. Note that because the apertures are linked to the breathing phases in our 4D planning scheme, the resulting treatment plans can only be delivered with the DRRT tumor tracking scheme, which maintains the association of aperture shapes and gantry angles to the breathing phases.

IV. C. Benefits of the 4D-IMAT planning scheme

Our 4D-IMAT planning scheme is based on a commercially available treatment planning system, and the DAD algorithm takes negligible time without using any extra computational power. A plan-evaluation process, which relies on the performance of the commercialized dose registration tool, normally can be completed within 20 min. Therefore, it is a beneficial approach to quickly generate 4D-IMAT solutions. A significant dosimetric benefit of our 4D-IMAT plans has been demonstrated compared to the 3D plans with IM. Thus, the effectiveness of our scheme in reducing margins is clearly indicated.

It is noteworthy that there exists a potential improvement for our 4D plans in OAR sparing which might be not attainable by our current planning scheme because of not optimizing on all breathing phases. Especially, when considering the varying relative distances between PTV and OARs throughout breathing, an ideal 4D optimizer should take advantage of mutual compensation among phases to achieve better plan quality (Chin *et al* 2011). For the future study, we would extend our 4D-IMAT planning scheme by further optimizing weights of phase-associated segments (i.e., redistributing MUs among phases) to achieve more OAR sparing. When doing so, we still would like to maintain the phase-segment association (i.e., delivery time of each segment), then resulting in higher delivered dose rate for phases with larger PTV-OAR distances.

Previous studies of free breathing of patients indicate large intra- and inter-fractional variations in breathing period and amplitude (Suh *et al* 2008). These variations in breathing motion can degrade the quality of delivered 4D-VMAT deliveries. Our 4D planning method is used to prepare a tracking delivery sequence while assuming a regular patient's respiratory pattern. Such a preprogrammed sequence is going to be delivered in the DRRT scenario, which compensates for the respiratory irregularities of patients. In DRRT delivery, the dose rates of planned phase-designated segments will be modulated to adapt to shortened (i.e., dose-rate increase) and prolonged (i.e., dose-rate decrease) breathing phases. Previous studies have shown the feasibility of DRRT by using an existing linac and dynamic MLC system for gantry-fixed fields (Yi *et al* 2008, Han-Oh *et al* 2009, Han-Oh *et al* 2010). Yang *et al* dosimetrically investigated the capability of DRRT in dealing with irregular breathing for fixed-gantry IMRT delivery. They demonstrated the advantages of DRRT technique in delivering preprogrammed plan sequences, i.e. DRRT could successfully compensate for variations in breathing periods. In addition, their case study indicated that, as long as the variations of breathing amplitude are within $\pm 20\%$ of the maximum amplitude in planning CT, the degradation of plan quality is dosimetrically insignificant.

Considerable range for dose-rate varying, which is needed in DRRT, has been available with current technology, i.e., flattening filter free (FFF) beams could provide dose rates of 1400–2400 MU/min. Because MLC-leaf motion is coupled to the delivered dose, a real-time increase of dose rate will result in a real-time increase of MLC speed, which might cause a beam hold if the MLC speed reaches the maximum. Therefore, in order to maintain DRRT's efficiency, a proper upper bound should be predetermined for MLC-leaf speed when generating the tracking sequence with our 4D planning method, allowing adequate room for leaf-speed increase. It is also noteworthy that, if gantry rotation is also constrained by the delivered dose, gantry-speed variation will be involved in the DRRT delivery. Thus, a feasibility study in gantry-speed variation in DRRT delivery should be furthered.

The deliverability of our 4D-IMAT plans for regular breathing has undergone a preliminary test (Niu *et al* 2011). With our planning method, commonly used clinical linear accelerators and MLCs can perform well in 4D-IMAT delivery. However, this testing is out of the scope of the present paper that centers on our planning method, so we will postpone further discussion of its results.

V. CONCLUSIONS

We have developed a new 4D-IMAT planning method that is simple in approach and straight-forward in practice. The dosimetric benefits of 4D-IMAT plans are clearly demonstrated in comparison to the common practice of adding a margin that encompasses the range of target motion. The method does not require significant additional computing power or time compared to 3D plans. The deliverability of our 4D plans is guaranteed by forcing connectivity between successive apertures considering the leaf-speed limit of an MLC. Such connectivity enforcement is shown not to cause significant degradation in plan quality or to increase delivery time.

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FIG. 1.

An example of segment-phase association of a single-arc plan. The treatment is delivered from the first segment starting at phase 0 (e.g., the end of inhalation). At the end of the first breathing cycle, the target moves back to phase 0 when the 10th segment is delivered.

FIG. 2. Diagram of truncating the travel of an MLC leaf for connectivity enforcement.

FIG. 3.
The simulated moving tumor near the diaphragm of a lung patient.

FIG. 4.

Two fragments (upper and lower) of 4D-IMAT plan for the simulated lung case. Each fragment represents several consecutive control points and the corresponding BEVs of PTV from inhalation (phase 0) to exhalation (phase 5). The angular separation between adjacent control points is 2° .

FIG. 5.

Isodose distributions of the individual phases (1–5) before and after DAD for the simulated lung case. For each phase, the isodose lines are plotted for 90%, 80% and 70% of the maximal dose of that phase.

FIG. 6.

A comparison of isodose distributions of different plans on the CT image set of the simulated lung case at phase 0 (the end of inhalation): (i) 3D plan on static patient; (ii) 3D plan on dynamic patient (i.e., before DAD); (iii) 4D plan on dynamic patient. The isodose lines (100%, 95% and 85% of the prescription dose) are plotted.

FIG. 7.

Forcing connectivity of leaf positions. Trajectories versus gantry rotation are plotted for two MLC leaves, i.e. (a) and (b). The corresponding leaf speed of (b) is shown in (c). Connectivity was enforced based on the leaf-speed limit of 2.5 cm/s.

FIG. 8.

A comparison of DVHs for the 4D plans with the 3D plans for all studied cases. The dashed line: the 3D plans on the static patients; the solid line: the 4D-IMAT plans; the dash-dotted line: the 3D plans with IM on the dynamic patients.

FIG. 9.

Value comparison of several dosimetric indicators between the plans for three case studeis. V₉₅ of PTV is the fraction of the PTV receiving at least 95% of the prescription dose. D₉₅ of PTV is the minimal dose received by 95% of most irradiated volume. The values of D₉₅ are normalized as the percentages of prescription dose to PTV. The conformity index is defined as the ratio of the extent of overlap between the PTV and the volume contained within 95% isodose line.

FIG. 10.

A comparison of isodose distributions of 4D accumulative dose on the CT image set of phase 0 for the 4D plans (left) and the 3D plans with IM (right). The isodose lines (95%, 50%, 35% and 20% of the prescription dose) are plotted.

Table 1

The value differences of major plan-quality indicators of 4D plans between after with before forcing connectivity for three case studies.

		Simulated lung case	Lung patient	Pancreas patient
PTV	$V_{95}(\%)$	-0.1	0.3	0.5
GTV	$V_{100}(\%)$	0.0	0.0	1.6
Lung	$V_{20}(\%)$	0.0	0.0	—
Liver	$D_{\text{mean}}(\text{Gy})$	0.0	—	0.0
Spinal cord	$D_{\text{near-max}}(\text{Gy})$	-0.1	-0.1	-0.2
Esophagus	$V_5(\%)$	-0.1	-0.1	—
Heart	$D_{\text{mean}}(\text{Gy})$	0.0	0.0	—
Small bowel	$D_{35}(\text{Gy})$	—	—	0.0
Left kidney	$D_{50}(\text{Gy})$	—	—	0.0
Right kidney	$D_{50}(\text{Gy})$	—	—	0.1

Note: $D_{\text{near-max}} = D_2$, the minimal dose received by 2% of the most irradiated volume.

Table 2

The dosimetric comparison of OARs between three schemes for three case studies. In each cell, the data are listed in the order of schemes “gold standard” 3D/4D(tracking)/3D with IM.

		Simulated lung case	Lung patient	Pancreas patient
Lung	$V_{20}(\%)$	9.6/10.6/13.7	13.3/12.7/18.1	—
Liver	$D_{\text{mean}}(\text{Gy})$	3.1/2.5/5.5	—	3.2/3.8/3.5
Spinal cord	$D_{\text{near-max}}(\text{Gy})$	7.7/8.0/10.0	12.5/11.8/11.0	12.8/13.1/16.3
Esophagus	$V_5(\%)$	51.2/42.9/59.2	53.0/47.9/49.8	—
Heart	$D_{\text{mean}}(\text{Gy})$	8.2/9.0/8.4	7.1/5.9/8.7	—
Small bowel	$D_{35}(\text{Gy})$	—	—	8.3/7.8/11.2
Left kidney	$D_{50}(\text{Gy})$	—	—	8.2/8.0/8.4
Right kidney	$D_{50}(\text{Gy})$	—	—	10.8/10.5/11.1