Inverse-planned deliverable 4D-IMRT for lung SBRT

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Purpose: We present a particle swarm optimization (PSO)-based technique to create deliverable four-dimensional (4D = 3D + time) intensity-modulated radiation therapy (IMRT) plans for lung stereotactic body radiotherapy (SBRT). The 4D planning concept uses respiratory motion as an additional degree of freedom to achieve further sparing of organs at risk (OARs). The 4D-IMRT plan involves the delivery of an order of magnitude more IMRT apertures (~15,000–20,000), with potentially large interaperture variations in the delivered fluence, compared to conventional (i.e., 3D) IMRT. In order to deliver the 4D plan in an efficient manner, we present an optimization-based aperture sequencing technique.

Method: A graphic processing unit (GPU)-enabled PSO-based inverse planning engine, developed and integrated with a research version of the Eclipse (Varian, Palo Alto, CA) treatment planning system (TPS), was employed to create 4D-IMRT plans as follows. Four-dimensional computed tomography scans (4DCTs) and beam configurations from clinical treatment plans of seven lung cancer patients were retrospectively collected, and in each case, the PSO engine iteratively adjusted aperture monitor unit (MU) weights for all beam apertures across all respiratory phases to optimize OAR dose sparing while maintaining planning target volume (PTV) coverage. We calculated the transition times from each aperture to all other apertures for each beam, taking into account the maximum leaf velocity of the multileaf collimator (MLC), and developed a mixed integer optimization technique for aperture sequencing. The goal of sequencing was to maximize delivery efficiency (i.e., minimize the time required to deliver the dose map) by accounting for leaf velocity, aperture MUs, and duration of each respiratory phase. The efficiency of the proposed delivery method was compared with that of a greedy algorithm which chose only from neighboring apertures for the subsequent steps in the sequence.

Results: 4D-IMRT-optimized plans achieved PTV coverage comparable to clinical plans while improving OAR sparing by an average of 39.7% for D_{max} heart, 20.5% for D_{max} esophagus, 25.6% for D_{max} spinal cord, and 2.1% for V_{13} lung (with D_{max} standing for maximum dose and V_{13} standing for volume receiving ≥ 13 Gy). Our mixed integer optimization-based aperture sequencing enabled the delivery to be performed in fewer cycles compared to the greedy method. This reduction was 89 ± 79 cycles corresponding to an improvement of $15.94 \pm 8.01\%$, when considering respiratory cycle duration of 4 s, and 55 ± 33 cycles corresponding to an improvement of $15.14 \pm 4.45\%$, when considering respiratory cycle duration of 6 s.

Conclusion: PSO-based 4D-IMRT represents an attractive technique to further improve OAR sparing in lung SBRT. Efficient delivery of a large number of sparse apertures (control points) introduces a challenge in 4D-IMRT treatment planning and delivery. Through judicious optimization of the aperture sequence across all phases, such delivery can be performed on a clinically feasible time scale. © 2018 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.13157]

Key words: 4D-IMRT, aperture sequencing, lung SBRT, mixed integer programming, particle swarm optimization

1. INTRODUCTION

Accounting for respiratory motion is one of the major challenges in delivering radiation therapy (RT) to patients with thoracic and abdominal cancer.^{1,2} Concerns about respiration-induced motion generally lead clinicians to treat a larger treatment volume, that is, internal target volume (ITV), which consequently increases the probability of toxicity in organs at risk (OARs). In lung stereotactic body RT (SBRT), where biologically potent radiation doses are administered to the tumor target in relatively few fractions,³ the potential for

overdose to normal structures and, therefore, radiation-induced toxicity is significantly higher than in conventionally fractionated RT. Thus, while SBRT achieves significantly superior outcomes compared to conventionally fractionated RT,⁴ increased risk of OAR toxicity limits the use of SBRT in patients with large and/or centrally located lung tumors.

One of the strategies proposed to improve OAR dose sparing is to use respiration-induced motion and deformation of thoracic organs and tumor, as observed from four-dimensional computed tomography (4DCT) simulation images, as an additional degree of freedom in treatment planning.^{5–9} We term

this approach as 4D planning and delivery. The term “4D” has been used for treatment planning and delivery strategies that use temporal information concurrently with 3D spatial information. For instance, conventional (i.e., 3D) ITV-based intensity-modulated RT (IMRT) plans are often referred to in the literature as “4D plans”. However, in this study, the term “4D” means that one explicitly accounts for the complex respiration-induced anatomical changes in the entire irradiated volume (tumor and OARs). In a conventional ITV-based IMRT delivery, for each beam, the total irradiation time in monitor units (MUs) is divided by the number of apertures corresponding to that beam. Thus, during delivery, the aperture shape is changed as a function of irradiation time. However, in our 4D-IMRT delivery, the aperture shape changes as a function of both irradiation time and the respiratory phase.¹⁰ In its current form, our technique accounts for anticipated motion (as seen during CT sim) and is distinct from respiratory gating where treatment plans are created for and delivered over fixed portions of respiratory cycle.¹¹ Our technique is also distinct from real-time multileaf collimator (MLC) tracking, where patient respiration is monitored during delivery to synchronize the treatment aperture with breathing in real time, thereby accounting for unanticipated motion.¹²

In previous studies, we introduced our 4D optimization strategy for conformal radiation therapy (CRT) planning^{5,9} and for inverse-planned respiratory phase gating.¹³ More recently, we reported on the implementation of particle swarm optimization (PSO) on a graphic processing unit (GPU)-based platform for 4D-IMRT employing a research version of a commercial treatment planning platform, Eclipse (Varian Medical Systems, Palo Alto, CA, USA).¹⁴ In our 4D planning approach, one 3D-IMRT treatment plan is created for each individual respiratory phase in Eclipse and MUs are optimized for all apertures in all respiratory phases simultaneously using the in-house GPU-enabled PSO engine.

Compared to 4D-CRT, 4D-IMRT utilizes more apertures to better conform to motion and deformation of the tumor. However, this advantage comes at the price of orders of magnitude higher complexity of optimization. In 4D-CRT, each beam usually has only one aperture (control point) per respiratory phase, whereas in 4D-IMRT, each beam usually has hundreds of apertures per respiratory phase. Delivering these many apertures purely sequentially would greatly increase the treatment time. It is important to reduce treatment time because patients may have difficulty lying on the treatment couch for long periods of time during radiation delivery resulting in increased risk of involuntary movements. Furthermore, longer fraction delivery times (≥ 15 min) are likely to significantly decrease cell killing.¹⁵ Finally, fast delivery also increases the number of patients treated using the same linear accelerator (Linac).¹⁶ Therefore, in addition to the dosimetric optimization, we also developed a technique to minimize the delivery time, thereby maximizing the delivery efficiency. For this purpose, we chose a mixed integer optimization-based aperture sequencing approach, where we minimize the time required to deliver the dose of a given

set of apertures. While several groups have reported on IMRT leaf sequencing based on fluence map optimization,^{17–19} MIOBAS is developed to optimize the sequence of apertures for which the shapes were preconfigured (in Eclipse), and MUs optimized in our in-house PSO engine. Note that while the PSO engine was implemented on GPUs, the MIOBAS module was implemented on the central processing unit (CPU) platform.

In the following sections, we describe our method, including patient cohort, data preparation, 4D-IMRT treatment plan optimization, and the aperture sequencing optimization (MIOBAS). Subsequently, we present results for both 4D-IMRT planning and aperture sequencing.

2. METHOD

Figure 1 describes the overall workflow of this study consisting of the steps performed in Eclipse treatment planning system (Section 2.B.1), our in-house GPU-based PSO inverse planning system (Section 2.B.2), and our in-house aperture-sequencing system, MIOBAS (Section 2.C). Appendix A (in Tables AI and AII) gives a glossary table for variables used in MIOBAS. The patient cohort and processing platform details are described in Sections 2.A and 2.D, respectively.

2.A. Patient cohort

Seven consecutive lung cancer patients were retrospectively selected for this study. Of these, six underwent lung SBRT (5 fractions, 30–60 Gy). One patient was initially prescribed SBRT, but upon further consideration by our clinical team, ended up receiving 45 Gy in 15 fractions. Figure 2 summarizes patient and prescription details.

2.B. PSO inverse planning

2.B.1. Data preparation

For each patient, we collected the clinical treatment plan, which was created on average CT scans using ITVs. In addition, for each patient, tumor and OARs were manually contoured on the CT volumes corresponding to end-exhalation (end-exhalation; i.e., 50%). The contours were then propagated from the 50% phase to other phases using Velocity (Varian, Palo Alto, CA, USA) image registration tool. Ten respiratory phases were considered, and the corresponding ten 3D-IMRT plans were generated in the Eclipse TPS V13.6 using the same beam configurations (gantry and couch angles) assigned by clinicians to the clinical ITV-based plans. In the individual-phase 3D-IMRT planning process, individual-phase target volumes were used in contrast to motion-inclusive target volumes used in a conventional ITV-based planning process. For each individual-phase 3D-IMRT plan, leaf sequencing was performed in Eclipse using Smart LMC (Leaf Motion Calculator); that is, apertures were sequenced for each beam at each phase independent of other phases. We

FIG. 1. Overall workflow of our proposed 4D-IMRT planning: We use three modules: Eclipse treatment planning system (TPS), PSO inverse planning, and aperture sequencing for deliverability (MIOBAS). [Color figure can be viewed at wileyonlinelibrary.com]

then exported $N_{\text{variables}} = N_{\text{apertures}} \times N_{\text{beams}} \times N_{\text{phases}}$ dose deposition matrices (one for each aperture) in order to optimize the dose contribution of each beam aperture to the irradiated anatomical volume (through optimizing its MU weight) as explained in the next subsection.

2.B.2. Optimizing aperture MU weights

Using our in-house optimization engine, the aperture MU weights for all beams across all respiratory phases (i.e., the ten 3D-IMRT plans) were optimized simultaneously such that dose deposited to OARs was minimized while the prescribed dose to the PTV remained at the required level. To use the respiratory motion as an additional degree of freedom rather than a hindrance, the algorithm could increase the MUs for a beam in one phase, in which due to respiration motion the tumor moved away from critical organs, and, reduce the dose in another phase in which tumor moved close to those organs. Therefore, the individual-phase 3D-IMRT plans were not necessarily delivering identical MUs.

The two following major calculation steps were involved in our aperture MU weight optimization^{5,14}:

Deformable image registration: We used an open-source deformable image registration (DIR) software, Elastix,²⁰ to sum up the dose across respiratory phases. As a one-time process, before starting optimization, deformable vector fields (DVF) were calculated from CT images for all respiratory phases to be mapped on the reference phase (end-exhalation).

During each iteration cycle of the MU weight optimization algorithm, the precalculated DVFs were applied to the dose matrices in a GPU-based parallelized implementation.¹⁴ Before optimizing the 3D-IMRT plans exported from Eclipse, we created an equal-weight summation of the doses from the ten 3D-IMRT plans on the reference phase using DIR. This plan is called 4D equal-weight plan.

Particle swarm optimization: The optimization algorithm optimizes aperture MUs across all respiratory phases simultaneously. PSO search methodology penalizes any violation of the dose–volume constraints, regardless of what form of penalty term is applied. To that end, it scans through phase–adjacent apertures and preferentially chooses to increase the weight for the apertures in respiratory phases where there are fewer OARs in the beam line, so as to reduce OAR dose. Such an approach eliminates or reduces the impacts of unwanted apertures, that is, those with more OARs in the beam line, by assigning a zero or lowered MU weights to them. As by-product, this approach results in sparsity or large MU variations between phase–adjacent apertures. While large variations in MUs of phase–adjacent apertures were avoided by some other groups (e.g., Nohadani et al.²¹) in order to guarantee deliverability, we rectified the impact of allowing such large variations by dividing large MUs into multiple pieces, similar to Gui et. al’s work,²² to be delivered over several breathing cycles in the sequencing step (Section 2.C). Similar to our previous works,^{5,14} we chose dose–volume limits that were stricter than institutional lung SBRT dose–volume constraints (protocols) to formulate our

Patient 1	Target Motion	15.0 mm		Patient 5	Target Motion	5.0 mm
	PTV	60.8 cc			PTV	49.81 cc	
	# Beams	9			# Beams	10	
	Prescribed Dose	60 Gy			Prescribed Dose	50 Gy	
	# Fractions	5			# Fractions	5	
Patient 2	Target Motion	7.0 mm		Patient 6	Target Motion	9.6 mm
	PTV	112.5 cc			PTV	16.06 cc	
	# Beams	11			# Beams	11	
	Prescribed Dose	60 Gy			Prescribed Dose	50 Gy	
	# Fractions	5			# Fractions	5	
Patient 3	Target Motion	3.5 mm		Patient 7	Target Motion	5.0 mm
	PTV	10.62 cc			PTV	479.4 cc	
	# Beams	8			# Beams	10	
	Prescribed Dose	30			Prescribed Dose	45 Gy	
	# Fractions	5			# Fractions	15	
Patient 4	Target Motion	4.5 mm
	PTV	21.46 cc					
	# Beams	10					
	Prescribed Dose	45 Gy					
	# Fractions	5					

FIG. 2. Coronal views with planning target volumes (PTVs) outlined in red (note yellow arrows) are shown for the seven patients of this study. Patient-specific maximum respiration-induced target motions and number of clinically assigned radiotherapy beams and fractions as well as prescribed PTV doses are also reported. [Color figure can be viewed at wileyonlinelibrary.com]

objective function (Appendices B and C). For each OAR within a patient, we considered multiple upper dose–volume limits corresponding to different partial volumes in order to obtain a better sparing than that in the clinical plan.

2.C. Aperture sequencing for deliverability

To formulate our aperture sequencing technique, we consider that the total delivery time for each beam is composed of time needed to deliver all apertures plus time needed to transition between apertures. We calculate these times separately in the following subsections.

2.C.1. Data preparation

Let N and M represent the set of apertures and the set of phases, respectively. For convention, we write that (j, i) denoted aperture i of phase j throughout this paper. Two crucial pieces of information are needed to ensure deliverability of an aperture sequence: time to deliver the prescribed dose in an aperture and time to change MLC shape between two

consecutive apertures. In what follows, we explain how to compute these times.

Let τ_{jib} denote the time needed to deliver aperture i of phase j in beam b , which is calculated as follows:

$$\tau_{jib} = \frac{\text{Prob}_j \times \text{MU}_b \times \text{ApertureWeights}_{jib}}{\text{Machine Dose Rate}}, \quad (1)$$

where MU of beam b (MU_b) and Machine~Dose~Rate was read from the individual-phase treatment plans and aperture weights were the output of PSO. Prob_j is the probability of respiratory phase j , which was calculated through a 2-min recording by bellows pneumatic belt (Philips Medical Systems, Andover, MA) acquired during 4DCT acquisition.

We calculated the transition time between every possible aperture pair for each beam. In each MLC leaf bank (Bank A and Bank B), there were K (normally, $K=60$) leaves. pos_{jik}^A and pos_{jik}^B denote the positions of leaf k of aperture (j, i) in Bank A and Bank B, respectively. Thus, $d_{bji}^{j' i'}$, the transition time to go from aperture (j, i) to aperture (j', i') in beam b , was calculated as:

$$d_{bji}^{j'i'} = \frac{\max\left(\max_{k=1,\dots,K}\left(\left|pos_{jik}^A - pos_{j'ik}^A\right|\right), \max_{k=1,\dots,K}\left(\left|pos_{jik}^B - pos_{j'ik}^B\right|\right)\right)}{V_{\text{leaf}}}, \quad (2)$$

where V_{leaf} is the leaf velocity for which we used the mechanical properties of the MLC. A maximum MLC leaf velocity of 3.5 cm/s (for the Varian MLC^{23,23}) was considered. In Eq. (2), we calculated the maximum distance the leaves must move to convert from aperture (j, i) to aperture (j', i') , and then by considering leaf velocity, we calculated the time needed for this transition.

We considered two respiratory cycle durations (T) in this study: 4 s and 6 s. To calculate the duration of each phase (e.g., t_j for phase j), we multiplied the probability of that respiratory phase j , denoted by Prob_j , by T . These probabilities were patient-specific.

2.C.2. Miobas

Figure 3 shows our overall sequencing workflow for both greedy and MIOBAS approaches. We started with reading intensity weights, beam MUs, respiratory phase durations, and transition times (between all possible pairs of apertures) for a given patient and plan. For each respiratory cycle, the optimized sequence of apertures was found, and the remaining aperture timings were updated; that is, if an aperture was completely delivered during that cycle, it was removed from further processing; Otherwise, the remaining required irradiation time (i.e., MUs) for that aperture's complete delivery was used in the next cycles of optimization. The difference between MIOBAS and greedy

approaches was the strategy each method used to create the sequence of the apertures in each respiratory cycle. MIOBAS found the optimal sequence using an optimization model (Section 2.C.3) while the greedy method moved from each aperture to its closest aperture in shape in neighboring aperture set. We considered the uniform dose rate delivery and allowed the apertures to be delivered in multiple respiratory cycles.²² Once the optimal sequence for one respiratory cycle was found, the MIOBAS algorithm moved on to the next respiratory cycle. This process was terminated when there were no apertures with undelivered MUs left. Since multiple respiratory cycles were required to complete the delivery of each beam, the respiratory phase loop was recursive.

Figure 4 illustrates a typical optimal sequence of apertures in one respiratory cycle highlighted in red, where one phase (Phase j) is skipped.

We compared the output of our proposed MIOBAS method with that of a greedy method. Typical solutions of both methods are presented in Fig. 5. In the greedy method, the next aperture to serve is chosen based on the shortest transition time in neighboring apertures. That is why a predictable pattern can be observed in the solutions of this method. On the contrary, MIOBAS could produce sequences of apertures that maximize the utilization time fraction, defined as the fraction of the respiratory cycle utilized for dose delivery.

FIG. 3. Workflow of the aperture sequencing system (MIOBAS). In finding the optimized aperture sequence in respiratory cycle k , the greedy method chooses only from neighboring apertures whereas our proposed method uses an optimization-based model which searches beyond neighboring apertures.

2.C.3. MIOBAS mathematical details

Here, we explain how we obtain the delivery-time-optimized sequence of apertures in a single respiratory cycle, where the best sequence is one that has the maximum delivery efficiency (maximum utilization time fraction). We first define the variables to formulate this optimization problem. Then, we explain the objective function and the constraints to solve this problem.

For beam b , to define a feasible sequence, we introduce four sets of binary variables:

- $w_{ji} = 1$ if aperture i is the first aperture of phase j in the sequence, and 0 otherwise;
- $z_{ji} = 1$ if aperture i is the last aperture of phase j in the sequence, and 0 otherwise;
- $x_{jii'} = 1$ if in phase j , aperture i' is the successor of aperture i in the sequence, and 0 otherwise; and
- $y_j = 1$ if phase j is to be skipped, and 0 otherwise.

We also introduced three continuous variables:

- S_{ji} , the start time of aperture i in phase j ;
- v_{ji} , the finish time of aperture i in phase j ; and
- p_{ji} , the time that MLC spends in aperture i in phase j .

In this formulation, the objective function aims at maximizing time spent on dose delivery rather than transitioning between apertures.

$$\text{Max} \sum_{j \in M} \sum_{i \in N} \tau_{jib} p_{ji} \quad (3)$$

In (3), also by multiplying p_{ji} by τ_{jib} in the objective function, the apertures are prioritized by their intensity weights,

so that those with larger weights are likely delivered earlier in the sequence. In our PSO 4D planning, we minimize violations of dose–volume constraints. A large aperture weight (and consequently, a large τ_{jib}) means that the respective aperture had less violation of dose–volume constraints. In other words, a large τ_{jib} means there were less OAR voxels in-line with radiation dose deposited by aperture i of phase j in beam b compared to other apertures. That is why the sequencing algorithm prioritizes aperture with larger weights.

A feasible sequence of apertures in a respiratory cycle should satisfy three major sets of constraints. First, in the dynamic MLC setting, apertures should be sequenced consecutively without any discontinuity in delivery. Second, the start and finish time of delivering an aperture should fall into its corresponding respiratory phase period. Third, the time difference between the finish time and start time of two consecutive apertures in a sequence should be no shorter than their calculated transition time. We formulate these constraints as follows

$$\sum_{i'} x_{jii'} + z_{ji} = \sum_{i'} x_{ji'i} + w_{ji}, \quad \forall (j, i), \quad (4)$$

$$\sum_i w_{ji} + y_j = 1, \quad \forall j, \quad (5)$$

$$\sum_i z_{ji} + y_j = 1, \quad \forall j, \quad (6)$$

$$\sum_{i'} x_{jii'} + z_{ji} \leq 1, \quad \forall (j, i), \quad (7)$$

Constraints (4)–(7) define a feasible path of apertures. Constraint (4) implies that if the MLC begins delivering an aperture, that aperture should be followed by either moving to another aperture in the same phase or moving to the

FIG. 4. The schematic display of apertures of a beam along with a sequence for three phases highlighted in red. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 5. A typical solution proposed by greedy (red) and MIOBAS (green) methods. [Color figure can be viewed at wileyonlinelibrary.com]

following phase. Constraint (5) imposes that a phase j is either chosen to be processed, in which case the first aperture to be visited is selected, or be skipped, in which case y_j should equal 1. Constraint (6) implies that a phase j is either chosen to be processed or be skipped. By constraint (7), we ensure that an aperture is not visited more than once in one respiratory cycle.

In addition to having a feasible path of apertures, we need to define timing of delivering the chosen apertures.

$$v_{ji} = S_{ji} + p_{ji}, \quad \forall(j, i), \quad (8)$$

$$\sum_{j'=1}^{j-1} t_{j'} \left(\sum_{i'} x_{ji'i} + w_{ji} \right) \leq S_{ji}, \quad \forall i, 1 < j \leq 10, \quad (9)$$

$$v_{ji} \leq \left(\sum_{j'=1}^j t_{j'} \right) \left(\sum_{i'} x_{ji'i} + w_{ji} \right), \quad \forall(j, i), \quad (10)$$

Equation (8) makes the finish time be equal to the start time plus the processing time. By constraint (9), we put a limit on the start time of an aperture, if it is chosen to be in the sequence in current respiratory cycle. Constraint (10) does the same thing for the finish time.

We also want to ensure that in each sequence, the transition time between apertures is considered properly:

$$S_{ji} \geq \max \left\{ \hat{v}_{im} + d_{bmi}^{ji} - T, 0 \right\} - T(1 - w_{ji}), \quad \forall i, j = 1, \quad (11)$$

$$v_{ij} + d_{bji}^{ii'} \leq S_{rj} + \left(T + d_{bji}^{ii'} \right) (1 - x_{jii'}), \quad \forall(j, i), (j, i') \quad (12)$$

$$v_{j'j'} + d_{bj'j'}^{ji} \left(\sum_{\forall k} x_{j'ki'} + w_{j'j'} \right) - \left(\sum_{s=1}^{j'+1} t_s \right) \left(1 - \sum_{\forall k} x_{jki} - w_{ji} \right) \leq S_{ji}, \quad \forall(j, i), (j', i') \quad (13)$$

The third set of constraints, (11)–(13), limits the transition time between selected apertures. In Eq. (11), $\hat{i}$ and $\hat{v}_{mi}$ denote the index and finish time of the last aperture processed in previous respiratory cycle, respectively. By introducing this constraint, we ensure that dose delivery does not occur during aperture-to-aperture transition. Equations (12) and (13) ensure that when the algorithm requires to choose an aperture from a different phase, it does so with minimal time expended by considering the leaf travel times for the aperture transition as well as the time difference between the current and the target phase.

Our formulation should account for cases where the calculated time for an aperture, τ , is longer than the corresponding

respiratory phase length. To manage this condition, we apply two constraints:

$$p_{ji} \geq \tau_{jib}^k \left(\sum_{i'} x_{ji'i} + z_{ji} \right) - r_{ji}, \quad \forall (j, i), \quad (14)$$

$$0 \leq p_{ji} \leq \tau_{jib}^k, \quad \forall (j, i), \quad (15)$$

And visit those apertures multiple times so as to ensure the assigned MU is delivered. Constraint (14) introduces a slack variable r_{ji} and allows delivery of a fraction of τ_{jib} . Suppose that the aperture is chosen to be delivered, that is, $\sum_{i'} x_{ji'i} + z_{ji} = 1$. In this case, constraint (14) could be rewritten as $p_{ji} + r_{ji} \geq \tau_{jib}$ which allows p_{ji} to take values less than τ_{jib} . Since p_{ji} has a positive weight in the objective function, the model tends to find the largest possible value for p_{ji} . However, p_{ji} cannot exceed the needed time τ_{jib} which is enforced in constraint (15). If MLC is not chosen to deliver (j, i) in a cycle, the model should have $\sum_{i'} x_{ji'i} + z_{ji} = 0$. Therefore, constraint (14) would be simplified as $p_{ji} + r_{ji} \geq 0$, which does not enforce anything because both p_{ji} and r_{ji} are positive by definition.

The signs and types of our variables are

$$S_{ji}, v_{ji} \geq 0, \quad \forall (j, i) \quad (16)$$

$$x, y, w, z \text{ binary} \quad (17)$$

If the intensity weight of an aperture is zero, p_{ji} will be zero for that aperture making all the related continuous and binary variables related to that aperture zero. Also, delivering phases consecutively is not always necessarily possible. For example, in some cases, the transition time between one aperture i in a respiratory phase $j - 1$ and all remained apertures of the following respiratory phase, j , is so long that none of the apertures of phase j are eligible to be delivered after aperture (j, i) . Or, in some cases while some apertures in phases $j - 1$ and $j + 1$ are left to be delivered, all apertures of phase j have already been sequenced. In the two above cases, phase j must be skipped. Assuming $N_{\text{apertures}} = 166$ (Eclipse default number of apertures used in our study), Fig. 4 illustrates this condition and a feasible sequence which traverses a *dummy aperture* designated in phase j to skip this phase. For this example, the sequence of apertures of phases $j - 1$, j , and $j + 1$ is as follows:

$$\dots, (j - 1, 1), (j - 1, 166), (j + 1, 165), (j + 1, 166), \dots$$

To skip phase j and obtain this sequence, the model will set

$$w_{j-1,1} = x_{j-1,1,166} = z_{j-1,166} = y_j = w_{j+1,165} = x_{j+1,165,166} = z_{j+1,166} = 1.$$

Therefore, to skip phase j , the model would have $y_j = 1$.

2.D. Processing platform

2.D.1. PSO inverse planning

The optimization engine was implemented in C++ CUDA on a hardware consisting of dual 8-core Xeon processors,

256 GB RAM, and four NVIDIA Tesla K80 general purpose GPUs (eight NVIDIA Kepler GK210 GPUs). We used Eclipse scripting interface (ESAPI) to generate dose matrices corresponding to apertures in Eclipse. The multi-GPU computing platform had a maximum processing capability of 8.5 Tflops per K80 card. Each GK210 had 12 GB of memory, totaling 96 GB of GPU memory for our whole system. This system had a nonuniform memory access (NUMA) architecture, where each CPU had direct access to their own system memory and PCI slots.

2.D.2. Aperture sequencing for deliverability

The MIOBAS proof-of-concept module was also implemented in C++ on the computing platform explained in the previous section (2.D.1), and the optimization was solved using Gurobi 7.02.²⁴

3. RESULTS

3.A. PSO inverse planning

Due to possibility of having zero weights, the number of apertures to be sequenced was smaller than the nominal number of apertures ($N_{\text{variables}}$). These numbers are displayed in Table I for our seven patients. No more than approximately 10% of apertures took nonzero weights.

Figure 6 shows dose-volume histogram (DVH) curves corresponding to the recreated clinical ITV-based plans, 4D PSO-optimized plans, and 4D equal-weight plans. Following our clinical practice, the ITV-based plans were created on average CT scans using our clinical protocol (see Appendix C). The 4D-optimized plans were created using our in-house optimization engine using dose constraints which were tighter than those applied in the clinic.

Following our clinic's practice, the plans were normalized to ensure 95% of PTV is covered by 100% of the prescribed dose. Although the 4D-IMRT plans did not necessarily have high dose sparing improvement for all OARs, Patients 1, 3, 4, and 6 experienced substantial improvements in dose sparing. Figure 7 gives a statistical demonstration of the improvements shown in Fig. 6. We calculated the percent improvement of OAR sparing in the 4D-IMRT PSO-optimized plans relative to the ITV-based plans for maximum dose (D_{max}) deposited in esophagus, heart, and spinal cord in all patients. For lung, the improvement was calculated for mean dose, V_{13} and V_{20} . We used the following relation to calculate the percent improvement for each OAR:

$$\begin{aligned} \text{percent improvement} \\ = \frac{\text{Dose of ITV} - \text{Dose of 4D optimized}}{\text{Dose of ITV}} \times 100 \end{aligned} \quad (18)$$

It can be observed that although, for some patients, lung received more doses, and in one patient, this was the case for spinal cord, the other OARs had consistent positive improvement.

The process time consists of two main parts: the optimization time with the PSO engine and the registration time with the DIR. The registration time is a one-time step which essentially extracts and stores the sparse dose matrices for each patient. Therefore, we only summarized the optimization time of the PSO engine in Table II.

3.A.1. Aperture sequencing for deliverability

Figure 8 compares the MIOBAS with the greedy method in terms of the total number of cycles required to deliver each plan over a (8a) 4-s respiratory cycle and (8b) 6-s respiratory cycle. Also, the relative improvement in efficiency using the proposed method is shown in the Fig. 8(c). The average and standard deviation of percent improvement yielded by our proposed method with $T = 4$ s were 15.94% and 8.01%, respectively. The average and standard deviation of percent improvement with $T = 6$ s were 15.14% and 4.45%, respectively. In Table III, we summarize the total delivery time in seconds for each patient considering greedy and MIOBAS methods, and in Appendix D, we report on utilization times per method in Table A3.

4. DISCUSSION

While lung SBRT has been demonstrated to be highly successful in achieving local control, the use of more potent (and, arguably more effective) SBRT fractionation schema and the administration of SBRT to more centrally located lesions are limited in practice because of potential toxicity to surrounding tissues.^{25,26} The applications of SBRT can be potentially further expanded by creating treatment plans with improved OAR sparing and, hence, lowered toxicity. The 4D planning concept can be independently applied to most commonly deployed treatment delivery techniques, that is, CRT,⁵ IMRT,²⁷ and volumetric arc therapy (VMAT).^{6,28}

Applying our group's previously developed 4D-IMRT inverse planning system to seven patients retrospectively, we observed the two following key specifications in the achieved results:

- Compared to the clinical ITV-based IMRT plans, OAR dose sparing was improved while PTV coverage was maintained (Fig. 6). Although not all of our patients benefited from 4D planning, Patients 1, 3, 4, and 6 showed remarkable sparing improvements comparing to their clinical plans (Fig. 7).
- While the PSO optimization process started with a large number of apertures, the number of apertures picked by

the optimization algorithm to be delivered was less by one, sometimes two orders of magnitude; that is, comparable to the number of apertures in ITV-based IMRT (Table I). This reduction makes the delivery problem much more tractable than if we had to deliver all possible 4D-IMRT apertures.

To enable and demonstrate the deliverability of 4D-IMRT plans, we developed a mixed integer optimization-based aperture sequencing method MIOBAS, which finds the best sequence of apertures for the MLC over each respiratory cycle, with minimal time spent in aperture–aperture transition. Several challenges were addressed. First, delivery of apertures should only take place in their associated respiratory phase duration. Second, large aperture MUs could be delivered in multiple respiratory cycles. Finally, zero-MU apertures were removed from the sequence without interrupting the delivery process.

In our study, for both 4D planning and aperture sequencing for delivery, we were limited by assuming that respiratory motion is fixed and reproducible — an assumption that is used in current clinical practice. Therefore, any intrafractional deviation from the assumed motion pattern due to irregularities such as amplitude or frequency changes, baseline shifts, and/or changes in the relative proportion of abdominal vs thoracic breathing, as well as phase discrimination errors could lead to geometric and dosimetric errors that adversely impact OAR sparing. A possible approach to address this limitation is to add a motion-related margin to each phase such that relatively minor deviations are covered, and a “beam-hold” signal which pauses dose delivery in case of larger deviations. Delivery time is relatively longer in 4D-IMRT because of the large number of apertures. Nevertheless, the improvements achieved in dose sparing of OARs make the proposed technique an attractive alternative to conventional IMRT. While short delivery times have been achieved by several radiotherapy techniques, such as RapidArc and VMAT, margin expansion is used for managing respiration-induced motion and deformation (i.e., ITV) limiting OAR sparing.

Our current MIOBAS model does not explicitly account for residual Mus; that is, while constraints (11)–(13) account for the transition time between aperture pairs, they do not consider MUs delivered during transition times between aperture pairs (residual MUs). For the seven patients of our study, we calculated these residual MUs in Appendix E and showed that they were a small fraction (<8.05%) of the prescribed MUs in the clinical plans in Appendix F. As a side note, we observed that the residual MUs were distributed almost uniformly across beams. One

TABLE I. Number of apertures for each patient's treatment plan, both nominal and PSO-created plans.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Nominal	14940	18260	13280	16600	16600	18260	11620
In PSO-created plan	1490	1790	1577	2202	2660	859	1339

FIG. 6. DVHs of the three following plans are compared: (1) Blue curves: 4D PSO-Optimized plans, which are created by employing the in-house PSO engine to optimize MU weights of the 3D IMRT plans created by the commercial TPS for the ten respiratory phases individually, (2) Red curves: 4D equal-weight plans, which are created through an equally-weighted summation of the individual-phase 3D IMRT plans, and, (3) Black curves: the clinical ITV-based IMRT plans, which are created by the commercial TPS. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 7. Box plots for percent improvement of doses deposited on OARs with 4D-IMRT PSO-optimized plans relative to ITV-based plans. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. PSO engine time to optimize MU weights.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Time (minutes)	77.5	69.7	69.8	82.3	79.1	79.3	73.5

FIG. 8. Total number of cycles for both the greedy and the MIOBAS approaches, and percent improvement of using the MIOBAS relative to the greedy for each patient with 4 and 6 s respiratory cycle time. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Total delivery time (in seconds) for each patient for greedy and MIOBAS methods using 4-s and 6-s respiratory cycle times.

Respiratory cycle	Sequencing method	Patients						
		1	2	3	4	5	6	7
4 s	Greedy	3188	2324	1164	1960	2556	672	924
	MIOBAS	2224	1936	1040	1512	2108	612	848
6 s	Greedy	3294	2454	1254	2040	2718	804	1140
	MIOBAS	2568	2070	1056	1662	2298	678	1038

possible approach to overcome this limitation is to modify the current MIOBAS formulation so as to calculate the residual MUs corresponding to transition between every possible aperture pair for each beam and include the calculated value in the MIOBAS objective function.

Alternatively, a more simplistic postsequencing approach is to assert beam-holds during the delivery whenever the apertures undergo transition.¹² Beam-holds could be applied for all transitions, or preferably, for transition times exceeding a predetermined MU threshold.

5. CONCLUSION

In this study, we proposed and developed a deliverable 4D-IMRT framework for lung SBRT to account for complex motion and deformation of the tumor target and OARs due to respiration. A research version of a commercial TPS was used to calculate dose deposition matrices, and a swarm intelligence-based algorithm was adopted to optimize the aperture fluence weights. Subsequently, a proposed mixed integer optimization-based sequencing method was developed to find the best sequence of apertures for every cycle of breathing while accounting for sparse fluence weights. Long delivery time required for some apertures was handled by delivering those apertures in multiple respiratory cycles. The results for seven lung cancer patients indicated that (a) OAR sparing was significantly improved, (b) the plans were deliverable, and (c) the sequences were significantly more efficient than the naïve greedy method. We have thus demonstrated the feasibility of 4D-IMRT as an attractive planning and delivery strategy to effectively manage respiratory motion during lung SBRT.

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CONFLICTS OF INTEREST

This work was partially supported through an in-kind equipment loan from Varian Medical Systems.

APPENDIX A

GLOSSARY TABLES

Tables AI and AII define the variables used in MIOBAS.

TABLE AI. Variables used as the input of the MIOBAS.

Name	Description	How obtained
τ_{jib}	The time needed to deliver the prescribed dose of aperture i of phase j in beam b	Calculated in data preparation
$d_{bj}^{i'}$	The transition time to convert MLC from aperture (j, i) of beam b to aperture (j', i') of the same beam	Calculated in data preparation
pos_{jik}^A	The position of leaf k of aperture i of phase j in Bank A leaves of MLC	Read from the output files of Eclipse TPS

TABLE AI Continued.

Name	Description	How obtained
pos_{jik}^B	The position of leaf k of aperture i of phase j in Bank B leaves of MLC	Read from the output files of Eclipse TPS
T	Length of respiratory cycle	Assumed to be either 4 or 6 s
t_j	Length of respiratory phase j	Calculated based on length of respiratory cycle and the probability of each phase in data preparation

TABLE AII. Variables used as the output of the MIOBAS.

Name	Type	Description
w_{ji}	binary	1 if aperture i is the first aperture of phase j in the sequence
z_{ji}	binary	1 if aperture i is the last aperture of phase j in the sequence
y_j	binary	1 if phase j of respiration is skipped
$x_{jii'}$	binary	1 if in phase j aperture i is succeeded by i' in the sequence
S_{ji}	continuous	the start time of aperture i in phase j
v_{ji}	continuous	the finish time of aperture i in phase j
p_{ji}	continuous	the time that MLC spends in aperture i in phase j

APPENDIX B

DOSE-VOLUME CONSTRAINTS

Let $N_{\text{structures}}$ be the number of structures considered in the planning. For each structure, multiple upper and lower bounds (indexed by f) and one maximum voxel-dose bound are introduced; $N_{\text{objective}_i^{\text{up}}}$ and $N_{\text{objective}_i^{\text{low}}}$ denote the number of upper and lower bounds for structure i , respectively. In this formulation, $D_{i,f}^{\text{up}}$, $D_{i,f}^{\text{low}}$, and D_i^{max} are used as the f th upper limit, lower limit, and maximum dose value, respectively, of structure i . For this structure, N_{voxels_i} is introduced as the number of voxels.

The PSO algorithm was employed to find the optimum aperture weights ($\mathcal{g}$) values which minimize the objective/cost function (F) modeled as

$$F = \sum_{i=1}^{N_{\text{structures}}} \frac{1}{N_{\text{voxels}_i}} \left(\sum_{f=1}^{N_{\text{objective}_i^{\text{up}}}} F_{i,f}^{\text{up}} + \sum_{f=1}^{N_{\text{objective}_i^{\text{low}}}} F_{i,f}^{\text{low}} + F_i^{\text{max}} \right) \quad (19)$$

where:

$$F_{i,f}^{\text{up}} = w_{i,f}^{\text{up}} \sum_{j=1}^{N_{\text{voxels}_i}} \left(D_j - D_{i,f}^{\text{up}} \right)^2 \cdot H(D_j - D_{i,f}^{\text{up}}), \quad (20)$$

$$F_{i,f}^{\text{low}} = w_{i,f}^{\text{low}} \sum_{j=1}^{N_{\text{voxels}_i}} (D_j - D_{i,f}^{\text{low}})^2 \cdot H(D_{i,f}^{\text{low}} - D_j), \quad (21)$$

$$F_{i,f}^{\text{max}} = w_i^{\text{max}} \sum_{j=1}^{N_{\text{voxels}_i}} (D_j - D_i^{\text{max}})^2 \cdot H(D_j - D_i^{\text{max}}) \quad (22)$$

In the above equations, we used the indicator function

$$H(y) = \begin{cases} 1, & \text{if } y \geq 0, \\ 0, & \text{if } y < 0, \end{cases}$$

where $w_{i,f}^{\text{up}}$, $w_{i,f}^{\text{low}}$, and w_i^{max} represent the patient-specific prioritizing factors for upper bound, lower bound, and maximum dose-related terms, respectively, in the objective function.

In Equations (20–22), the dose values D_j for each phase are calculated using DIR in the following equation:

$$D = \sum_{k=1}^{N_{\text{variables}}} \text{DIR}(\vartheta_k \times d_k), \quad \vartheta_k \geq 0, \quad (23)$$

where d_k represents the dose matrices of aperture k .

APPENDIX C

CLINICAL PROTOCOL FOR SBRT DOSE CONSTRAINTS

Five fractions	Volume	Volume max (Gy)	Max point dose (Gy)	Endpoint (≥Grade 3)
Serial tissue				
Spinal cord and medulla	<0.35 cc <1.2 cc	23 Gy (4.6 Gy/fx) 14.5 Gy (2.9 Gy/fx)	30 Gy (6 Gy/fx)	Myelitis
Spinal cord subvolume (5–6 mm above and below level treated per Ryu)	<10% of subvolume	23 Gy (4.6 Gy/fx)	30 Gy (6 Gy/fx)	Myelitis
Esophagus	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)	Stenosis/fistula
Heart/pericardium	<15 cc	32 Gy (6.4 Gy/fx)	38 Gy (7.6 Gy/fx)	Pericarditis
Parallel tissue				
Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic lung function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

APPENDIX D

UTILIZATION

TABLE AIII. Utilization timetable.

Patient	Respiratory cycle time (s)	Method	Utilization (%)	Improvement (%)
1	4	Naive	3.56	43.36
		Optimized	5.10	
	6	Naive	3.45	28.12
		Optimized	4.42	
2	4	Naive	4.97	20.04
		Optimized	5.96	
	6	Naive	4.70	18.55
		Optimized	5.58	
3	4	Naive	4.71	11.92
		Optimized	5.28	
	6	Naive	4.38	18.75
		Optimized	5.20	
4	4	Naive	4.71	29.63
		Optimized	6.11	
	6	Naive	4.53	22.74
		Optimized	5.56	
5	4	Naive	3.20	21.25
		Optimized	3.88	
	6	Naive	3.02	18.28
		Optimized	3.57	
6	4	Naive	0.52	7.39
		Optimized	0.56	
	6	Naive	0.41	12.88
		Optimized	0.46	
7	4	Naive	0.15	26.01
		Optimized	0.18	
	6	Naive	0.11	7.62
		Optimized	0.12	

The utilization time fraction, defined as the fraction of the respiratory cycle utilized for delivering apertures, is calculated as follows:

$$\text{Utilization} = \frac{\sum_{j,i} \tau_{jib}}{\text{CycleTime} \times \sum_b (\text{NumberOfCycles})_b} \times 100,$$

where the index b represents the beams. The utilization is calculated for each method (naïve or optimized). Let U_{naive} and $U_{\text{optimized}}$ denote the utilization of naïve approach and optimized approach, respectively. The rightmost column shows the percent improvement of the utilization of the optimized method with respect to the utilization of the naïve method which is obtained with the following calculation:

$$\text{Improvement} = \frac{U_{\text{optimized}} - U_{\text{naive}}}{U_{\text{naive}}}$$

APPENDIX E

CALCULATING RESIDUAL MU

Two hypothetical apertures in a 4D-IMRT are shown in Fig. A1. Suppose we want to calculate the residual MU to transition from aperture 1 to aperture 2.

Let N_{leaf} denote the number of leaf pairs in each aperture. In the example of Fig. A1, for the sake of brevity, we only considered $N_{\text{leaf}} = 12$, but in our experiments with Eclipse, we set $N_{\text{leaf}} = 60$. Suppose for a leaf pair k , the distance between left and right leaf is denoted as a_k^1 and a_k^2 for apertures (j, i) and (j', i') , respectively, as shown in Fig. A2. In this figure, a_{kl} and a_{kr} is written for the distance that left leaf and right leaf should move from Aperture 1 to Aperture 2.

FIG. A1. Two apertures in an 4D-IMRT. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. A2. Distance of k th leaf pairs in Aperture 1 and Aperture 2. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. A3. Residual MU per beam for Patient 1 and Patient 7. [Color figure can be viewed at wileyonlinelibrary.com]

For linear accelerators, Task Group 71 of the Therapy Physics Committee of the AAPM²⁹ defines 1 MU as machine calibration dose rate when 1 cGy is delivered at the depth of maximum dose on the central axis (d_{max}) for a 10×10 field with 100 source surface distance (SSD). Therefore, given a field with size s , one could calculate the MU delivered in t minutes with the following formulation:

$$R = \frac{s}{100} \times t \times V_{\text{MU}}. \quad (24)$$

where V_{MU} is the machine dose rate per minute.

As displayed in Fig. A2, we break calculation of the residual transition MU into three parts: (1) the residual MU of moving left leaf a_{kl} mm, (2) the residual MU of moving right leaf for a_{kr} mm, and (3) the residual MU deposited in a

$\min(a_k^1, a_k^2)$ long field during the total transition time from aperture (j, i) to (j', i') . Therefore,

$$R_k = F_k(a_{kl}) + F_k(a_{kr}) + G_k(a_{kl}, a_{kr}),$$

where

$$F_k(a) = \int_0^a \left(\frac{x}{V_{\text{leaf}}} \times \frac{w_k}{100} \times V_{\text{MU}} dx \right)$$

and

$$G_k(a, a') = \frac{\min(a, a') \cdot w_k}{100} \cdot V_{\text{MU}} \cdot d_{bji}^{j'i'}.$$

V_{leaf} and V_{MU} denote the leaf velocity (which we considered 3.5 cm/s in our experiments) and machine dose rate (which we assumed 600 MU/min) and w_k denotes the width of the k th leaf pair. Also, $d_{bji}^{j'i'}$ (defined in Section 2.C.1) is the transition time from aperture (j, i) to (j', i') in beam b . In $F_k(a)$, the first term in the integral, $\frac{x}{2 \cdot V_{\text{leaf}}}$, calculates time required for leaves to displace a a long field. The term $w_k \cdot dx$ basically gives the field size which should be scaled by $\frac{1}{100}$.

The total residual MU can be then calculated by $TR = \sum_{k=1}^{N_{\text{leaf}}} R_k$.

APPENDIX F

RESIDUAL MU RESULTS

For the seven patients of study, we calculated total residual MU presented in Table AIV.

TABLE AIV. MU calculated by clinical plan, residual MU deposited in transition times, and the ratio of residual to clinical in both 4-s and 6-s respiratory cycle.

	Clinical plan	4-s respiratory cycle		6-s respiratory cycle	
		Residual transition	Ratio (%)	Residual transition	Ratio (%)
Patient 1	2228.9	100.5	4.51	89.1	4.00
Patient 2	2101.5	57.5	2.74	53.5	2.55
Patient 3	1217.5	9.4	0.77	9.2	0.76
Patient 4	6719.2	5.6	0.08	5.3	0.08
Patient 5	2570.2	40.0	1.56	40.2	1.56
Patient 6	2116.7	13.1	0.62	13.6	0.64
Patient 7	1151.4	92.5	8.04	89.3	7.75

For Patient 1 and Patient 7 who had the most residual MUs, we display the bar charts of residual MU per beam in Fig. A3. The plots show that the residual MUs are almost uniformly distributed among all the beams in these cases.

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