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Inverse 4D conformal planning for lung SBRT using particle swarm optimization

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Abstract

A critical aspect of highly potent regimens such as lung stereotactic body radiation therapy (SBRT) is to avoid collateral toxicity while achieving planning target volume (PTV) coverage. In this work, we describe four dimensional conformal radiotherapy (4D CRT) using a highly parallelizable swarm intelligence-based stochastic optimization technique. Conventional lung CRT-SBRT uses a 4DCT to create an internal target volume (ITV) and then, using forward-planning, generates a 3D conformal plan. In contrast, we investigate an inverse-planning strategy that uses 4DCT data to create a 4D conformal plan, which is optimized across the three spatial dimensions (3D) as well as time, as represented by the respiratory phase. The key idea is to use respiratory motion as an additional degree of freedom. We iteratively adjust fluence weights for all beam apertures across all respiratory phases considering OAR sparing, PTV coverage and delivery efficiency. To demonstrate proof-of-concept, five non-small-cell lung cancer SBRT patients were retrospectively studied. The 4D optimized plans achieved PTV coverage comparable to the corresponding clinically delivered plans while showing significantly superior OAR sparing ranging from 26% to 83% for $D_{\max}$ heart, 10% to 41% for $D_{\max}$ esophagus, 31% to 68% for $D_{\max}$ spinal cord and 7% to 32% for V_{13} lung.

Keywords

4D treatment planning; lung SBRT; optimization; stochastic

1. Introduction

The management of respiratory motion is one of the major challenges of modern thoracic and abdominal radiation therapy [1, 2]. Motion-induced translation, rotation and deformation of the tumor and surrounding organs at risk (OARs) can cause significant geometric and dosimetric errors [3–6]. In hypofractionated regimens such as lung stereotactic body radiotherapy (SBRT), the impact of such errors is amplified. SBRT administers high, biologically potent radiation doses to the tumor target in relatively few fractions (typically, 3–5 fractions compared to 30–40 for conventionally-fractionated lung radiotherapy). Lung SBRT has been shown in multicenter studies to yield a 5-year primary tumor control above 90% in inoperable Stage I non-small-cell lung cancer (NSCLC) patients [7]. Nevertheless, limitations in current respiratory motion management techniques and the

consequent geometric and dosimetric uncertainties limit the wider application of SBRT [8]. These uncertainties are typically accounted for by a motion-encompassing internal target volume (ITV) expansion of the tumor target [9–11]. Such expansion causes irradiation of healthy surrounding tissues and critical structures and hence, can lead to moderate-to-significant radiation toxicity [12–14].

In order to overcome these limitations and potentially expand the scope of lung SBRT, we describe a 4D (3D + time) optimization strategy for conformal radiotherapy (CRT) treatment planning. The key idea is to use respiratory motion as an additional degree of freedom rather than a hindrance. The optimization task is to achieve greater OAR-sparing while maintaining PTV coverage and delivery efficiency. Delivery efficiency is defined as the percentage ratio of beam apertures which have non-zero monitor unit (MU) weights to the total number of beam apertures in a treatment plan. The ultimate goal, beyond the current scope, is to combine such 4D-optimized plans with motion-synchronized dynamic multileaf collimator (DMLC)-based 4D dose delivery.

Several studies in the literature focus on using inverse planning through optimizing intensity weights either for beamlets (bixels or rays) or apertures [15, 16]. The former is termed as fluence optimization and the latter, as fluence-weight optimization. Each intensity weight is translatable to a monitor unit (MU) which defines the time duration of the corresponding beam ON. Our present scope is limited to 4D CRT planning through optimizing aperture fluence-weights. Despite noticeable improvements in plan quality which have been shown to be achievable through inverse planned 3D CRT [17], typically, 3D CRT plans are generated using forward planning [16]. We generate our 4D CRT plans using inverse planning due to the need to optimize over a significantly larger solution space. For CRT planning, terms such as ‘beam weight’ or ‘field weight’ have also been used to refer to aperture fluence-weight in the literature [18]. For brevity, we call aperture fluence-weights as aperture weights throughout this paper.

The majority of the 4D planning studies in the literature are focused on intensity modulated radiotherapy and volumetric modulated arc therapy (IMRT and VMAT); however, the computational techniques can be translated and compared to 4D CRT, which is studied in this work. One popular approach to reduce the computational complexity in 4D planning is to initiate the planning process by creating a single optimized 3D plan for a single respiratory phase (reference phase). The reference optimized 3D plan is then translated to other respiratory phases using tumor displacement and deformation in configuring MLC leaf trajectories for each individual-phase plan. This technique has been widely used in 4D IMRT planning [19–23]. In some studies, similar methodology is used while respiratory phases are prioritized based on the time duration of each phase [24, 25]. In such studies, although the computational load is reduced by partially confining major optimization tasks to a single respiratory phase, 4D optimization is not utilized to its full capacity. Therefore, there is significant scope for improving plan quality. Comprehensive 4D planning studies in the literature consider optimizing plans across respiratory phases while taking deliverability constraints into account. These techniques have also been mainly used for IMRT and VMAT planning [26–29].

Here, we do not propagate a single optimized plan on a reference phase to all phases, as in [19–25]. In contrast, to have a true 4D CRT plan, the treatment plan is optimized over ten respiratory phases simultaneously. Therefore, the optimization problem is large. However, our approach is simplified in the following ways:

1. Instead of creating apertures based on optimized fluence maps, as in [26–29], we employ apertures which are pre-configured by a commercial treatment planning system and adjust the corresponding MU weights; thus, simplifying and speeding up the optimization process. This initial plan consists of ten individual-phase deliverable 3D plans created based on 4DCT scans and is our good “first-guess” introduced to the optimization algorithm.
2. We do not avoid zero-weighted apertures which enforce beam-holds and degrade delivery efficiency; however, we introduce delivery efficiency as a parameter inside the optimization process in order to allow the planner have control on permissible population of zero-weighted apertures, and avoid or allow delivery options close to gating. Since we optimize for all beams across all phases, beam-specific gated plans can be created where each beam is gated at a different respiratory phase.
3. We do not avoid large MU variations in phase-adjacent apertures. Such large variations have been avoided in Nohadani et al.’s work to guarantee deliverability [26]. Our approach, therefore, can result in degraded delivery efficiency if variable dose rate delivery is not considered as a delivery option.

Similar to current clinical paradigms, we do not explicitly account for cycle-to-cycle variations in respiration; i.e. the motion captured in the 4DCT is assumed to represent the motion during treatment. Furthermore, we do not explicitly test the deliverability of the obtained leaf sequences.

One source of complexity in 4D planning arises from the non-convexity of the optimization solution space which is generally rendered by dose-volume objectives [18, 30, 31]. The main impact of non-convexity is multiple local minima in the solution space. Some studies suggest that, due to degeneracy, the non-convexity in radiotherapy planning optimization does not cause a significant issue [32]; however, we believe that the way an objective function is framed defines how significant the roles of non-convexity and degeneracy are [33]. One way to manage non-convexity is by limiting computation of dose-volume objectives to intervals in between consecutive convex optimization steps [34]. Our approach, however, is to use an optimization technique designed for non-convex problems. Particle swarm optimization (PSO) is a highly-parallelizable stochastic global optimization algorithm. PSO was first introduced by Eberhart and Kennedy in 1995 [35] and has been benchmarked over time in a variety of large-scale, non-convex mathematical problems [36, 37]. Global optimization techniques have previously been applied to lung radiation therapy problems. For instance, Li et al. have used PSO for 3D IMRT beam-angle selection [38], while Yun et al. have estimated lung tumor motion using an artificial neural network-based

method [39]. To the best of our knowledge, this is the first use of PSO in 4D aperture-weight optimization.

2. Methods

2.A. Patient Data

Respiratory-correlated 4DCT scans, each comprising ten CT volumes corresponding to ten respiratory phases, were collected retrospectively from five early stage NSCLC SBRT patients. While the patients were clinically treated by 3D CRT, here we investigated 4D CRT, where one CRT plan per each respiratory phase was created using 4DCTs and all plans were optimized simultaneously. Table 1 gives a summary of the clinical plans and tumor characteristics for these patients. These patients were chosen from our clinical lung SBRT population, which comprised of early-stage NSCLC patients. Abdominal compression was applied for two of the patients. While compression is standard-of-care for lung SBRT in our clinic when tumor motion exceeds 0.5cm, some of the patients in this cohort were unable to tolerate compression. Two of the lesions were peripherally located and others centrally (within 2 cm of the proximal tracheobronchial tree).

Prescribed SBRT dose ranged from 50 to 60 Gy, administered over 3 or 5 fractions. Figure 1 gives a visual representation of beam configurations in the corresponding clinical plans. The number of radiation beams varied between 9 and 12. Cases 3, 4 and 5 represent treatment plans where beams passing through some OARs were difficult to avoid. For patients 1 and 2, tumors were smaller in size.

For individual-phase plans, the PTV was generated by isotropically expanding the margins of the GTV (gross tumor volume) by 5 mm. For clinical plans, the PTV was generated by a 5 mm expansion of the ITV. Figure 2 highlights the motion-induced margin expansion of the target in sample axial, sagittal and coronal slices for each of the five patients. Figure 2 also shows a 2D view of tumor position with respect to OARs.

Data preparation for 4D planning was performed as follows. For each patient, the target and normal organs were manually contoured on the CT volume corresponding to end exhalation (50%). The contoured structures were propagated from 50% phase to other phases using Velocity, a commercial deformable-image-registration tool (Varian Medical Systems, Palo Alto, CA). Corresponding ten 3D conformal plans were generated in the Eclipse treatment planning system (Varian Medical Systems, Palo, Alto) using the same beam configurations (gantry and couch angles) as the clinically delivered plans. Individual-phase structures (OARs and PTV) were used for creating these 3D individual-phase plans. A vendor-provided scripting interface (Varian Medical Systems) was used to create and export 3D dose matrices corresponding to each aperture in Eclipse. The total number of apertures was equal to the number of phases multiplied by the number of beams. This work was focused on CRT plans; therefore, there was only one aperture per beam. Figure 3 shows a flowchart of the process.

2.B. Deformable Image Registration

To sum up the dose across respiratory phases, we had to account for intrafraction organ motion and deformation. NiftyReg, an open-source image-registration package, was integrated with our in-house optimization software to perform the deformable image registration [40, 41]. As a one-time process, before starting optimization, deformation vector fields (DVF) were calculated from CT images for all respiratory phases to be mapped on the reference phase. End exhalation (50%) respiratory phase was considered as reference phase. During each iteration cycle, the pre-calculated DVFs were applied to the dose matrices. Note that, this step could not be shifted to before starting the iteration loop because nonlinear deformation operation would render the original aperture weights irretrievable. The quality of registration was verified using the Dice similarity coefficient [42]. Dice coefficients were larger than 0.83 (average: 0.97 and standard deviation: 0.02) for all the structures of interest in our patient cohort.

By default, the Eclipse treatment planning system has a coarser spatial resolution for dose matrices [$2.5 \times 2.5 \times 2 \text{ mm}^3$] compared to that for CT images [$1.17 \times 1.17 \times 2 \text{ mm}^3$]. In this work, we resampled the CT images to match the spatial resolution of the dose matrix before applying deformable image registration.

2.C. Dose Comparison Strategy

Dose-volume histograms (DVHs) were used to compare the 4D optimized plans with clinical plans. However, we had to take contouring and dose calculation uncertainties into account. The contouring uncertainties came from non-identical contouring procedures followed for creating ITV-based clinical plans and 4D plans. The two contouring procedures are briefly summarized as follows:

- For clinical ITV-based plans, ITV was contoured manually by dosimetrist on maximum intensity projection (MIP) CT scan. PTV_{ITV} was created by expanding ITV margins homogeneously by 5mm. Body organ contours and treatment plans were created on average CT scan.
- For 4D plans, GTV and body organs were manually contoured on 50% respiratory phase CT scan by dosimetrist. PTV was created by expanding GTV margins homogeneously by 5mm. Tumor and body organ contours were propagated to other respiratory phases using deformable image registration (see Figure 3).

The clinical PTV_{ITV} should ideally be identical to the union of individual phase PTVs; however, significant uncertainties are introduced due to inter-user variability. Table 2 shows the volume discrepancies between the contours in the clinical plans and the 4D plans for the 5 patients of this study.

To eliminate contouring uncertainties in our comparison, we recreated ITV-based plans while taking motion-induced variations into account. We introduced '4D summation method' to closely follow our 4D planning approach (Figure 3) in the recreation of ITV-based plan. In 4D summation method,

- PTV_{ITV} was created by superimposing PTVs of all individual-phase plans.
- PTV_{ITV} was copied on the 10 individual-phase CT scans.
- The individual-phase body organ contours were kept same as those in 4D planning.
- 10 individual-phase plans were created in Eclipse using the original, clinically-assigned beam configurations. Beam apertures were made to be conformal to PTV_{ITV}. Acuros dose calculation engine was used to calculate the dose for each phase.
- The final ITV-based plan dose was calculated by summing up the dose over ten phases using deformable image registration.

We believe that 4D summation method gives the most accurate estimation of dose to PTV_{ITV} and OARs. Therefore, we used the 4D summation results as our “clinical” baseline.

We have also compared our results with 4D equal-weight method where aperture weights of the clinical plan are used for all respiratory phases and aperture shapes are made conformal to the individual-phase PTVs. 4D equal-weight plan was also used as a reasonable first guess for optimization.

2.D. Optimization Details

The exported dose matrices were fed into the optimization algorithm as inputs. Using PSO, the individual aperture weights were iteratively adjusted and used to scale the corresponding dose matrices toward achieving a desired treatment plan.

2.D.1 Objective Function—The PSO algorithm was employed to find optimum aperture weight (x) values which minimized the objective/cost function (F) modeled as

$$F = \rho_{(x)} \times \sum_{i=1}^{N_{structures}} \frac{1}{N_{voxels}^i} (F_{i(V_i^{HD} \geq V_i^{UP})}^{Upper\ limit} + F_{i(V_i^{LD} \leq V_i^{LOW})}^{Lower\ limit} + F_i^{maximum\ point\ dose}) \quad (2)$$

where

$$\begin{cases} F_i^{Upper\ limit} = w_{u_i} \sum_{j=1}^{N_{voxels_i}} (D_j - D_{max_i})^2 \cdot H(D_j - D_{max_i}) \\ F_i^{Lower\ limit} = w_{l_i} \sum_{j=1}^{N_{voxels_i}} (D_j - D_{min_i})^2 \cdot H(D_{min_i} - D_j) \\ F_i^{maximum\ point\ dose} = w_{m_i} \sum_{j=1}^{N_{voxels_i}} (D_j - D_{max_i}^p)^2 \cdot H(D_j - D_{max_i}^p) \\ D = \sum_{l=1}^{N_{phase}} DIR(\sum_{k=1}^{N_{apertures}} (x_k^l \times d_k^l)) \quad x_k^l \geq 0 \end{cases} \quad H(y) = \begin{cases} 1 & y \geq 0 \\ 0 & y < 0 \end{cases} \quad (3)$$

and

$$\rho_{(X)} = \begin{cases} 1 & \eta_{(X)} \geq \eta_{min} - 1 \\ \eta_{min} - \eta_{(X)} & otherwise \end{cases}$$

$$\eta_{(X)} = \frac{N_{x>0}(x \in X)}{N_{phase} \times N_{apertures}} \times 100, \quad X = \{x_1^1, \dots, x_{N_{apertures}}^{N_{phase}}\} \quad (4)$$

In the above equation sets, $N_{structures}$, N_{voxels} , $N_{apertures}$, N_{phases} and $N_{x>0}$ represent the number of structures, the number of voxels for each structure, the number of apertures per phase, the number of respiratory phases and the number of non-zero apertures, respectively. As expanded in Eq. (3), $F^{Upper\ limit}$ and $F^{Lower\ limit}$ are the volume-based maximum and the volume-based minimum dose objectives. These volume-based terms make the objective function non-convex [43]. V^{HD} is the volume within a structure that receives higher doses than an assigned volume-based maximum dose (D_{max}). $F^{Upper\ limit}$ is calculated and included in the cost function only if V^{HD} is larger than a corresponding predefined volume of V^{UP} . Similar volume and dose parameters (V^{LD} , D_{min} and V^{LOW}) are considered for calculating $F^{Lower\ limit}$. The penalty for maximum voxel dose is calculated in $F^{maximum\ point\ wise}$ for any voxel which receives a dose surpassing a predefined D_{max}^p . Maximum point dose penalty is not a volume-based cost term. Note that although we have shown only one upper and one lower dose cost term per structure in Eq. (2), any number of dose-volume cost terms can be added to the summation.

In Eq. (3), H is the Heaviside function and D_j is the total dose accumulated in the j^{th} voxel. The dose matrices corresponding to individual apertures are summed, after applying appropriate deformation and scaling. d and x are the dose deposition matrix and the weight for each aperture. Deformation operator, which is shown by DIR , maps all floating phase doses on a single reference phase.

D_{max} , V^{UP} , D_{min} , V^{LOW} and D_{max}^p are defined based on our clinical lung SBRT protocol. Table 3 summarizes our institutional dose-volume limits for lung SBRT which slightly varies from RTOG 0813[44] in the case of spinal cord and esophagus. Note that, “Lung” refers to total lung volume minus GTV. The prioritizing factors w_U , w_L and w_m are user-defined and patient-specific. They can be set differently for each optimization cost term.

ρ is the delivery efficiency penalty which is calculated as shown in Eq. (4). We added ρ in our objective function to let users have control on the percentage of apertures that are turned off (weighted zero). A zero-weighted aperture means there is no irradiation through that aperture during corresponding respiratory phase. Zero-weighted apertures can prolong delivery time. To clarify, a traditional 3D CRT plan will have a delivery efficiency of 100%, while a gated delivery that delivers dose between 40%–60% phase will have a delivery efficiency of 30%. $\rho = 1$ means the number of ON apertures are equal to or larger than that required to maintain minimum delivery efficiency (η_{min}). To keep the penalty larger than 1, efficiency differences less than 1 are not considered. Figure 4 shows how delivery efficiency penalty changes with the number of ON apertures in an arbitrary scenario.

Note that the treatment planning problem is typically degenerate; i.e., there are several solutions that lead to plans with similar objective values [10, 33]. However, by adding more

dose-volume constraints to the objective function equation and limiting delivery efficiency, fewer solutions correspond to an identical objective value.

2.D.2 Optimization Technique—4D optimization is a large problem; e.g., in this study, the number of variables was between 90 and 120. Also, the problem is non-convex. With these requirements in mind, PSO was chosen as the optimization engine. In general, stochastic global optimization techniques such as PSO are well-suited for large-scale, non-convex problems due to their potential for escaping local minima [45]. However, these algorithms tend to be computationally intensive. A major advantage of PSO over its counterpart algorithms, such as genetic algorithms and neural networks, is its intrinsic parallelizable computational structure combined with relatively simple control gears. [37].

The details of PSO are explained in the literature [36, 46], and briefly summarized herein. PSO, as the name indicates, imitates the behavior of a swarm of bees, a flock of birds or a group of fish in their food searching activities. Its main idea resides in incorporating a balance of group learning, individual cognition and random decision making in the search process. The search for an optimum solution initiates with multiple random guess solutions, which are introduced as starting particle positions inside the solution space. Particles are, in fact, the individual search agents employed to explore the solution space and look for optimum solution. The moving engine of the swarm is a velocity function which is defined by three forces: 1- an inertia force allowing the particles to keep searching in their previous moving direction, 2- a cognitive force allowing each particle to follow its own best experience (personal best), and 3- a social learning force encouraging the particles to move toward the swarm's synergy (global best). The significance of each force in defining a particle's next step is influenced by both deterministic and random coefficients.

Figure 5 summarizes the PSO implementation for this study. An absorbing wall boundary condition was used, meaning that particles that “flew out” of bounds were neither discarded nor reflected. They were stopped and given new chances to fly back inside the solution space [47]. The solution space boundaries were confined by setting a maximum allowable MU for apertures. A maximum allowable number for iterations of 25 was also predefined, so that the optimization process could be terminated even if the minimum objective threshold of zero was not met.

For PSO, swarm population size (number of particles) should generally be large enough to sample and explore the solution space sufficiently. Based on problem complexity, the population size can be any number between a fraction and multiples of the variable number [48]. In our 4D planning problem, the number of dose-volume objectives (i.e., discontinuities in solution space) defined the problem complexity and swarm population size. We chose the swarm population (15 particles) to be well larger than the number of dose-volume objectives. The number of unknowns was 100, 120, 100, 110 and 90 for the five patients.

Particle positions in PSO are typically initialized by random spreading based on a uniform distribution. In this study, the starting position of one particle was predefined using our “first good guess” which was the equal-weight plan. In the equal-weight plan, aperture weights of

the 3D clinical plan were assigned to all individual-phase plans. The starting positions for all other particles were defined randomly. To help PSO particles explore the large solution space more efficiently, one extra step, illustrated in Figure 5 via the expanded view of step 3, was added in calculating the objective function. A so-called “critical objective” was defined and used to generate a surrogate objective function in order to reduce the swarm search effort. The surrogate objective function was designed to assign a feasible solution to particles flying into infeasible space. The details of this solution space modification technique have been described in [49]. The condition of “having 95% of PTV covered by 100% of the prescribed dose” was deemed as the critical objective. Note that infeasible solutions are those violating the critical objective.

2.D.3 Priority Factors and Delivery Efficiency—One of the challenges in inverse planning is to define the priority factors for the objective function (w_d , w_l and w_m in Eq. (3)). The challenging part is their being case-dependent. In this work, we used fixed values which were adjusted manually through trial and error. Dose-volume limits were chosen to be stricter than those shown in Table 3 to set more challenging objectives for optimization. We also assigned a high priority factor to sharp dose fall-off for PTV. Multiple upper limit objectives were chosen per OAR (per patient) to get a better plan compared to clinical plan. Lung V_{20} has been shown to be a predictive value for the development of pneumonitis in conventionally fractionated lung radiotherapy practices. However, using biological effective dose (BED) equation [50, 51], V_{20} for 30 fractions is translated to $V_{11.5}$ and $V_{13.5}$ for 3 and 5 fractions, respectively. Some other studies have used $V_{12.5}$ for SBRT [52]. In our optimization, we chose V_{10} , V_{13} and V_{20} to account for the objectives in that neighborhood. Mean dose is not considered as an optimization limitation in our clinic for lung SBRT; therefore, we did not use it. The minimum allowed delivery efficiency (η_{min}) was set to 50%. for Patients 4 and 5 who presented more challenges to the optimization process due to the tumors being located in close vicinity of OARs and having relatively smaller motion (see Table 1). For other patients η_{min} was 70%. In calculating η_{min} , a threshold of 0.5 was considered for defining zero MU weights.

2.E. Processing Platform

The current proof-of-concept code was implemented in MATLAB (R2013b), using the parallel processing toolbox. The computer workstation had dual-3.1GHz Xeon processors (8 cores per processor with hyperthreading ON = 32 cores). The code was parallelized over PSO particles. Results

2.F. Optimization

Table 4 compares doses to OARs from the 4D optimized plans and the ITV-based clinical plans. All percent differences (%) are rounded to the nearest integer. DVH curves corresponding to the recreated clinical ITV-based plans, the 4D optimized plans and the corresponding 4D equal-weight plans are shown in Figure 6.

It was observed that the PSO-based 4D SBRT plans kept PTV coverage within the acceptable range and significantly improved dose-sparing for parallel and serial OARs. On

average, maximum dose to spinal cord, heart and esophagus was reduced by 48%, 48% and 27%, respectively. Overall improvement in lung V_{13} was 20%.

In almost all cases, dose sparing improvement gained by 4D equal-weight plan was less than that achieved by 4D optimized plan. For patient2, however, dose sparing for heart was better in 4D equal-weight plan as compared to 4D optimized plan. In that case, the optimization sacrificed slight improvement in heart dose for larger gains in esophagus and spinal cord sparing.

Figure 7 shows how setting different minimum delivery efficiencies changed the optimization behavior and 4D planning results for one of the patients of this study (Patient1). To have a better comparison study, DVH results for ITV-based plan with gating delivery at the end of exhalation are also shown in Figure 7. Comparing DVH curves of the clinical plan for Patient1 in Figure 6 (red curves, first row) with those of gating in Figure 7, it is seen that, as expected, gating improves PTV sharp dose fall off as well as OAR sparing. More importantly, Figure 7 shows that:

- The proposed 4D technique achieved dosimetrically comparable results with single-phase (end-of-exhale) gating for $\eta_{min} = 100\%$; i.e., delivery efficiency of 100%, compared to a delivery efficiency of 10% for the gating strategy. In practice, the delivery efficiency of gating is improved by expanding the gating window (e.g., to 3 phases); however, this will be accompanied by a reduction in plan quality due to ITV expansion and, potentially, increased OAR dose.
- A noticeably large enhancement of esophagus sparing was achievable between $\eta_{min} = 10\%$ and $\eta_{min} = 100\%$, which is a demonstration of the effect of the additional degree of freedom introduced in the proposed 4D planning through η_{min} .
- In general, a 4D plan with $\eta_{min} = 10\%$ is not necessarily equivalent to a traditional single-phase gating since our proposed optimization algorithm can create beam-specific gating where each beam is gated in a distinct phase.

In our clinic, ITV-based plan dose is normalized to ensure 95% of PTV_{ITV} is covered by 100% of the prescribed dose. Therefore, in Figure 6, DVH for PTV_{ITV} is shown for the ITV-based plans while for the 4D plans, DVH for individual-phase PTVs deformed and summed on the reference respiratory phase (50%) are shown. To give an example, Figure 8 shows the difference between the DVHs for abovementioned PTVs for Patient 1 in the ITV-based clinical plan. The DVH for 4D optimized plan is also repeated in Figure 8 for the sake of an easier visual comparison.

Finally, Figure 9 shows the optimized aperture weights for an arbitrary beam for each of the five patients. As the aperture weight increases, beam-on time increases.

3. Discussion

3.A. 4D Planning Technique

SBRT is a proven successful lung cancer therapy and has made a tremendous impact on public health in recent years. Hypofractionation, in general, offers higher effective dose to tumor and leads to enhanced local tumor control [53]. Nonetheless, in current clinical practice, the use of more potent prescriptions of lung SBRT is limited due to potential toxicity to surrounding tissues [54]. To expand the application range of SBRT, it is necessary to create treatment plans with improved OAR-sparing and consequently lower toxicity. Theoretically, OAR-sparing can be improved by maneuvering dose distribution using additional degrees of freedom. IMRT and VMAT, for instance, provide such additional degrees of freedom by introducing a larger number of apertures and beam angles. 4π radiotherapy using gantry-mounted linacs is a more recent technique which also introduces extra degrees of freedom through presenting non-coplanar beam geometries [55]. 4D planning adds even more degrees of freedom by bringing time dependency into the picture. 4D planning is inherently applicable to a variety of treatment delivery techniques, such as CRT, IMRT and VMAT [26–29, 56]; however, the degrees of computational complexity varies by technique.

In this study, we used 4D inverse planning to improve CRT plans. The dose-sparing improvements were achieved through fluence weight optimization for apertures, which were pre-calculated in ten 3D individual respiratory phase treatment plans using 4DCTs. Although weight optimization is a simplified version of fluence optimization introduced in the literature (e.g., [26, 27]), the results shown here appear to be encouraging. It was shown in our results that OAR-sparing could be slightly improved by merely eliminating motion-inclusive margin expansion of tumor target and creating 4D equal-weight plans; however, optimizing the aperture weights further enhanced the OAR-sparing. Weight optimization offers a more computationally simplified 4D planning compared to full-fledged 4D fluence optimization by skipping aperture shape optimization process. Our current study focused on 4D conformal radiation therapy where fluence weight for one aperture per beam was optimized over phases. More complex delivery techniques such as sliding window IMRT or VMAT come with higher computational complexity in 4D planning. The number of variables (apertures) for 4D-IMRT and 4D-VMAT can be in the tens of thousands. The significance of employing a parallelizable technique such as PSO and implementing it on massively parallel architectures comprising general purpose graphic processor units (GPUs) then becomes even more sound [57, 58]. Therefore, our future work for higher-dimensional planning and optimization will likely be focused on GPU implementations of PSO.

A stochastic global optimization technique was employed to solve the problem. Five clinical SBRT cases with 9 – 12 beams were optimized over 10 respiratory phases. The optimization goal was to reduce OAR dose compared to corresponding ITV-based clinical plans and also to satisfy compliance with our institutional SBRT clinical guidelines. We showed substantially improved OAR dose-sparing for lung V_{13} , spinal cord D_{max} , esophagus D_{max} and heart D_{max} by maximums of 30%, 62%, 49% and 89%, respectively. Of course, the magnitude of OAR sparing through 4D planning is expected to be patient-specific and

dependent on tumor motion and location. In our clinic, abdominal compression is standard-of-care for lung SBRT when tumor motion exceeds 0.5cm; therefore, our patient cohort exhibited relatively small tumor motions. We expect larger improvements in treatment plan qualities for free breathing cases.

One of the challenges of treatment planning optimization is to define appropriate priority factors for optimization terms. These factors are user-specific and case-dependent [59]. Different methods have been presented in the literature to select appropriate priority factors. Some studies have used fixed priority factors over the entire optimization process [60], while others pursue flexible approaches, such as interactive [61] and adaptive methods [62, 63]. The priority factors can be assigned based on the organ distance from the tumor [64, 65] or based on quantified objective violations. Objective violations are either handled at the organ level [34] or voxel level [60, 66]. In this study, we used fixed priority factors and manually adjusted them based on how reachable each objective was. Automation and adaptive adjustment of priority factors, if introduced in the algorithm, can considerably reduce the user's effort.

3.B. Deliverability

While we did not intend to study aperture-sequencing and/or delivery methods in the present work, a rough assessment of the deliverability can be given here. Our initial individual-phase 3D plans were created in Eclipse treatment planning system where leaf sequencing was done for each. The PSO algorithm adjusted the aperture weights and did not alter the aperture shapes; however, our optimization did not avoid zero weighting or sharp variations between the weights of phase-adjacent apertures.

On the delivery side, zero-weighted apertures impose beam-holds which degrade the delivery efficiency by increasing the delivery time. Nonetheless, as Figure 7 shows, there is a merit in this approach as it can improve the OAR sparing by introducing aperture-specific gating. While in some instances, our algorithm chose to turn the beam ON in only one or few phases, these instances were distinct from clinical respiratory gating. In our case, the phases for which the beam was on could be different for each field (e.g., beam 1 – phase 10%, beam 2, phase 50%, etc.). In the case of clinical respiratory gating, the beam is turned on during the same respiratory phase (typically exhale) for all fields, which is not necessarily the optimal solution.

The delivery options for our proposed planning technique could be

- Uniform dose rate delivery (implementable in current clinical setting): Large intensities are divided to multiple pieces and delivered over several breathing cycles assuming that the patient's breathing is reproducible within reasonable thresholds. Such division of large MUs over several breathing cycles has been previously suggested by other researchers; e.g., [23]. Some other researchers have avoided large intensity variations in phase-adjacent apertures for the sake of deliverability [26].
- Variable dose-rate delivery, which can be adapted with some technical and hardware modifications as a near future delivery option. Since this

technique is currently being used in VMAT [31], its fundamentals have already been developed and can potentially be extended to other delivery techniques.

3.C. Motion Uncertainty

One limitation of our study was that the respiratory motion was considered to be fixed and reproducible. Consequently, possible causes of geometric and dosimetric errors, such as motion variations, respiration irregularities, breathing frequency changes, baseline shifts and amplitude variations were not considered [67]. To address this limitation in our study, it is possible to add a reasonable user-defined, phase-specific margin to accommodate relatively minor deviations from the 4DCT-recorded respiratory cycle and apply beam-hold only when the deviations are larger than that threshold (see Appendix).

4. Conclusion

In this work, a 4D planning strategy was introduced to optimize aperture weights across respiratory phases. The optimization task was to improve OAR sparing while PTV coverage is maintained and delivery efficiency is controlled. A commercial treatment planning tool was used for dose calculation and a swarm-intelligence-based algorithm was applied to optimize the large-scale non-convex problem. The optimization results for five CRT lung cancer patients were presented with significant OAR sparing improvement.

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Appendix

To address motion uncertainty, it is possible to add a reasonable user-defined, phase-specific margin to accommodate relatively minor deviations from the 4DCT-recorded respiratory cycle. In Figure 10, we show a simplified scenario where tumor is considered to be spherical. We have created an extended margin of $R' - R$ along the main tumor motion direction (superior/inferior) and shown in Table 5 that such margin could save in the extra volume getting irradiation, as compared to the traditional ITV practice. Table 5 considers a motion of 1 cm and a margin of 5 mm. Figure 11 gives an example of how such margin could be created in Eclipse.

Figure 12 compares extra radiated volumes, measured in Eclipse. It is observed that, despite large tumor volumes in this study, a margin of $\sim 5mm$ can be safely added to compensate for motion uncertainties. The unexpectedly large gain for Patient3 is because of the tumor's irregular shape (see Figure 11).

Figure 1.
3D views of beam central axes, tumor and OARs for the five patients.

Figure 2.

Axial, sagittal and coronal views for (a) Patient1, (b) Patient2, (c) Patient3, (d) Patient4 and (e) Patient5 are shown in right, middle and left panels of each row, respectively. Contours for spinal cord, heart, esophagus and PTV are highlighted. PTV contours are shown for the clinical plan (PTV_{ITV}) as well as those of the end of exhalation (PTV_{50%}). The dimensions are in mm.

Figure 3.
4D optimization (a) procedural and (b) algorithmic workflow

Figure 4.
 ρ for a scenario where 120 apertures are considered and $\eta_{min} = 70$

Figure 5.
PSO algorithm used in this study

Figure 6.

DVH comparison between ITV-based, 4D equal-weight and 4D optimized plans for the five SBRT patients. Each row is related to one patient and each column is related to one structure. DVH curves for the ITV-based plans recreated by 4D summation method are shown in red. DVH curves for the 4D equal-weight and 4D optimized plans are shown in black and green, respectively.

Figure 7.

DVH comparison between 4D optimized plans with minimum delivery efficiencies of 10% (magenta) and 100% (blue) and also gated clinical plan at the end of exhale (orange) for Patient 1.

Figure 8.

PTV DVH comparison between 4D optimized plan with minimum delivery efficiency of 70% and ITV-based plan considering both PTV_{ITV} and actual PTV at 50% respiratory phase. The three graphs are normalized to 95% PTV coverage with 100% prescribed dose.

Figure 9.
Optimized aperture weights for one arbitrary beam

Figure 10.

Simplified comparison between extra volumes irradiated when considering (a) ITV approach (), and (b) 4D phase-specific motion-extension (δ) for an ideally-shaped spherical tumor

Figure 11.

PTV margin extension performed in Eclipse treatment planning system for Patient 3 (having the largest tumor in this study). PTV contour on phase 00% (end-of-inhale), PTV contour on phase 00% with phase-specific margin extension and PTV contour created from ITV are shown in red, green and purple colors, respectively.

Figure 12.
Comparing extra volumes irradiated when considering PTV_{ITV} versus PTV with phase-specific margin extension (for phase 00%) in 4D planning for the 5 patients of this study.

Table 1

Patient-specific RT planning information

	Patient1	Patient2	Patient3	Patient4	Patient5
Number of beams	10	12	10	11	9
Number of fractions	3	3	5	5	5
Prescribed dose (Gy)	54	54	60	50	60
GTV (cc)	14.4	24.5	110.2	45.6	43.5
PTV ITV (cc)	40.8	59.7	213.0	112.5	104.1
Maximum PTV motion at the center of mass (cm)	1	1	0.8	0.7	0.6
Tumor site	Right upper lobe - Peripheral	Left upper lobe - Peripheral	Right upper lobe - Central	Left upper lobe - Central	Left upper lobe - Central
Abdominal compression	No	Yes	Yes	No	No
Abdominal compression motion (cm)/(GTV (cc)	0.069	0.040	0.007	0.015	0.014

Table 2

Volume differences due to contouring

	Structure Volume (cc)									
	Patient1		Patient2		Patient3		Patient4		Patient5	
	Clinical*	Union**	Clinical	Union	Clinical	Union	Clinical	Union	Clinical	Union
PTV	40.8	35.7	59.7	58.6	213.0	203.4	112.5	123.9	104.1	103.0
Lung	2790.9	3018.2	4259.3	4306.1	7101.9	7090.3	2723.7	2971.2	2353.0	2612.4
Esophagus	31.6	46.9	47.7	72.2	42.7	63.1	30.6	43.4	27.8	38.2
Spinal Cord	79.5	85.9	23.0	35.4	34.2	34.8	57.0	61.4	62.9	64.2
Heart	739.1	895.7	632.2	818.4	1004.7	1166.1	632.0	739.8	1142.3	1322.7

* Manually contoured on average CT by dosimetrist

** Union (superimposition) of individual-phase contours used for 4D planning

Table 3

Institutional lung SBRT dose-volume constraints

		3 fractions			5 fractions		
Organ At Risk (OAR)		Volume (V ^{UP})	Volume Max (Gy)	Max Point* Dose (Gy)	Volume Max (Gy)	Max Point Dose (Gy)	
Serial Tissue	Spinal Cord and medulla	<0.35 cc	18	21.9	23 14.5 23	30	
		<1.2 cc <10%	18				
	Esophagus	<5 cc	17.7	25.2	19.5	35	
	Heart	<15 cc	24	24	32	38	
Parallel Tissue	Lung	<1500cc <1000cc	10.5 11.4	NA**	12.5 13.5	NA**	

Volume (V ^{LOW})		Volume Min (Gy)	Max Point Dose (Gy)	Heterogeneity
Tumor	95%	Prescribed Dose	~1.5 × Prescribed Dose	Allowed

* Point is defined as 0.035cc or less.

** NA: Not Applicable

Dosimetric comparison between the ITV-based plans recreated by 4D summation and optimized 4D plans

Table 4

Dosimetric Criteria	Patient1			Patient2			Patient3			Patient4			Patient5		
	ITV	4D	% (I)	ITV	4D	%	ITV	4D	%	ITV	4D	%	ITV	4D	%
Heart D_{max} (Gy)	11.3	1.9	83	4.6	3.4	26	2.6	1.1	58	11.5	8.3	28	31.1	16.3	48
Esophagus D_{max} (Gy)	16.4	9.6	41	20.2	15.3	24	29.3	17.5	40	37.8	34.2	10	34.7	27.4	21
Spinal Cord D_{max} (Gy)	6.5	2.1	68	16.1	7.9	51	24.3	10.5	57	14.4	9.3	35	26.8	18.4	31
Lung $V_{13}^{(2)}$ (%)	15.9	13.5	15	14.6	10.0	32	19.6	13.3	32	18.9	17.6	7	16.4	14.2	13

(1) % stands for improvement percentage and is defined as $100 \times (value^{ITV} - value^{4D}) / value^{ITV}$.

(2) V_{13} is the percentage volume receiving doses higher than or equal to 13Gy.

Table 5

Extra volumes irradiated considering the two scenarios shown in Figure 10

$d = 1\text{ cm}$		$R' - R = 1\text{ mm}$	$R' - R = 2\text{ mm}$	$R' - R = 5\text{ mm}$
$R(\text{cm})$	$^*(\text{cm}^3)$	$\delta^{**}(\text{cm}^3)$	$\delta(\text{cm}^3)$	$\delta(\text{cm}^3)$
2	12.3	2.7	5.5	15.9
4	50.0	10.3	21.2	56.8
8	200.8	40.7	82.4	213.9

$$^* \Delta = \frac{4}{3}\pi R^3 - \frac{\pi}{12}(4R+d) \times (2R-d)^2$$

$$^{**} \delta = \frac{4}{6}\pi(R'^3 - R^3)$$