Published in final edited form as:

Phys Med Biol. 2010 September 7; 55(17): 5189–5202. doi:10.1088/0031-9155/55/17/019.

Motion management with phase-adapted 4D-optimization

Omid Nohadani¹, Joao Seco², and Thomas Bortfeld²

Omid Nohadani: nohadani@purdue.edu; Joao Seco: jseco@partners.org; Thomas Bortfeld: tbortfeld@partners.org

¹ School of Industrial Engineering, Purdue University, West Lafayette, IN 47907, USA

² Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA

Abstract

Cancer treatment with ionizing radiation is often compromised by organ motion, in particular for lung cases. Motion uncertainties can significantly degrade an otherwise optimized treatment plan. We present a spatiotemporal optimization method, which takes into account all phases of breathing via the corresponding 4D-CTs and provides a 4D-optimal plan that can be delivered throughout all breathing phases. Monte Carlo dose calculations are employed to warrant for highest dosimetric accuracy, as pertinent to study motion effects in lung. We demonstrate the performance of this optimization method with clinical lung cancer cases and compare the outcomes to conventional gating techniques. We report significant improvements in target coverage and in healthy tissue sparing at a comparable computational expense. Furthermore, we show that the phase-adapted 4D-optimized plans are robust against irregular breathing, as opposed to gating. This technique has the potential to yield a higher delivery efficiency and a decisively shorter delivery time.

1. Introduction

Intensity-modulated radiation therapy (IMRT) has the advantage of delivering highly conformal dose distributions to tumors of geometrically complex shapes. However, uncertainties can degrade the quality of treatment plans, so much so that an otherwise optimal plan may turn out clinically unacceptable. These uncertainties can have numerous sources, such as an imperfect setup during the treatment, imaging errors, dosimetric errors and organ motion. The issue of respiratory motion, causing displacements of planning volumes, has been recently addressed using robust optimization techniques, amongst others by Chu *et al* (2005) and by Chan *et al* (2006).

In general, motion uncertainties can occur in different stages. Since IMRT plans are delivered in multiple fractions, issues can arise due to interfraction or intrafraction motion of tumor and organs. In this work, our main focus is on intrafraction motion, as caused by breathing during irradiation. Goitein (2004) discusses various aspects of intrafraction motion and argues that many of the conclusions are applicable to interfraction motion as well. While patient immobilization, active breathing control and abdominal compression are techniques to limit the motion, there is still some residual motion. With regard to issues at the tumor periphery, geometrical margins can be added to account for residual motion.

Parallel to this, there are two competing objectives: on the one hand, there is a need for increasing the dose to the tumor in order to improve tumor control. On the other hand, there is a desire to decrease the dose to the normal tissue in order to minimize complications, which translates in reduced margins. Tracking has been proposed to account for the intrafraction motion by temporally adapting the beam direction to the current position of the tumor, resulting in a synchronized motion of the beam with the tumor (Keall 2004). In

principle, the tumor motion relative to the room coordinates can be compensated either by moving the beam or moving the patient (displacement of the couch). Using a dynamic multileaf collimator (MLC), as described by Keall *et al* (2001), facilitates the tumor tracking and allows the patient to remain stationary. Note that the accuracy of the tracking is limited by leaf thickness of the MLC, while adjusting the couch position enables higher accuracy which can be reduced due to patients' reactive displacement. Moreover, tracking requires a significantly more complicated delivery procedure. Nevertheless, tracking offers higher degrees of freedom.

Another approach is gating, where the radiation is delivered only during a certain time frame, matched to the corresponding breathing phases. Trofimov *et al* (2005) provide a comparison between different procedures: (i) gating based on an optimized breathing window, (ii) planning based on optimized margins, (iii) optimized tracking and (iv) the motion kernel approach, which uses a more accurate dose deposition of pencil beams to moving targets. They show that enlarged margins yield to a substantial increase of the integral dose to patient. Furthermore, they argue that the shortcoming of gating includes the increased treatment duration. Moreover, since optimized gating plans are always related to a particular window, the outcomes are intrinsically sensitive to inaccuracies in the gated window which might result in severe overdose to healthy tissue. We will address the issue of sensitivity in section 4.4. Note that all these approaches require to some extent the precise knowledge of the motion, which is not always a realistic assumption.

In this study, we present a novel time-resolved, thus, 4D-IMRT optimization technique based on Monte Carlo dose calculation that takes into account all phases of breathing and minimizes the overall dose subject to (i) lower bounds for tumor voxels and (ii) upper bounds for remaining voxels, and (iii) closeness of the beamlet intensities for neighboring breathing phases. The advantages of this method are that it

- provides treatment plans that are inherently robust against motion uncertainty;
- allows us to reduce margins;
- can warrant for deliverability of the final plan and, thus, is also robust against delivery uncertainties that might arise from sequencing errors or simple MLC positioning errors and
- will lead to increased delivery efficiency and shorter delivery time.

To demonstrate the performance of the proposed robust method, we apply our phase-adapted 4D-optimization method to two lung cancer cases which exhibit a sizable displacement of the tumor due to respiratory motion. We chose these cases in order to cover a broad spectrum of examples, i.e. a patient with a smaller tumor and large amplitude of motion to represent a worst-case scenario (we refer to as patient 1) and a patient with a large tumor and small amplitude of motion (patient 2) to cover the other end of the spectrum. We compare the outcomes of the phase-adapted 4D-optimization method with those of the gating method. The information on motion is collected based on time-resolved CT scans. These 4D-CT data are registered to the free breathing reference phase. To best account for lung tissue inhomogeneities, we use Monte Carlo dose calculation. The plans are quasi-static, because we constrain the phase variation of the corresponding beam intensities in order for the plan to be robust and deliverable.

Obviously, the quality and deliverability of any IMRT plan depend on how well the intensity maps can be sequenced into leaf positions. The method of direct aperture optimization takes these sequencing effects into account *a priori* (Shepard *et al* 2002). However, these have to be either restricted to a small subset of possible apertures, as discussed by McQuaid and Webb (2008), or they are computationally very expensive. It is beyond the scope of this

study to address possible deviations of the planned dose distribution from the corresponding distribution after the leaf sequencing. We therefore consider the dose distribution of our optimal fluence intensities as the final delivered distribution.

2. Materials and methods

2.1. 4D-data collection

The time-resolved 4D-CT data are acquired on a GE lightspeed Qx/I 4-slice CT scanner. A current of 170 mA is used for the thorax scan for the 140 kV tube potential. The CT slice thickness is 2.5 mm. The gross target volume contouring was conducted by visual inspection of the tumor motion on all phases. We will describe the addition of margins in detail when we discuss the different planning modalities in section 4.

The RPM system records the respiratory motion in the axial cine-mode. The reconstructed CT scans are retrospectively sorted into volumes containing the phase information of patient's breathing. The amplitude of the tumor motion is approximately 25 mm for patient 1 and 15 mm for patient 2, both of which are mostly in the superior–inferior direction. We divided the 4D-CT images in six significant phases, such that each phase has the same likelihood to occur based on the pre-treatment RPM signal. They are denoted by SE0%, SE20%, SE40%, SE50%, SE60% and SE80%. Note that SE0% and SE50% are the inhale and the exhale phases in the respiratory cycle, respectively. Consequently, SE20% and SE40% are phases that are leading from inhale to exhale, and SE60% and SE80% are phases leading from exhale to inhale. Since the phases are sufficiently separated and the perturbations of the probability mass for each phase are significantly smaller than their actual value, it is justified to assume that the phases have in average the same probability density over the course of the treatment.

For the dose calculation, we include organ deformation, which constitute nonrigid motion. The dose cubes for each phase are registered to the end of exhale volumes, using deformable image registration. We employ a *B*-spline deformable registration method, as discussed by Rueckert *et al* (1999), which is based on the Insight Segmentation Registration Toolkit. We compute the deformation vector using *B*-spline interpolation from the deformation values of points located in a coarse grid, which was a 50 mm cube. An expert identified homologous points in the end of the inhale phase as well as in the end of the exhale phase. These points were matched with *B*-spline at an accuracy of 4.21 ± 2.42 mm in the lungs of both patients.

2.2. Dose calculation

In an earlier work, imaging errors as they affect the dosimetry and dosimetric errors as caused by approximative dose calculations were addressed using stochastic optimization (Nohadani *et al* 2009). However, to avoid interplay of possible dosimetric uncertainties with motion and in order to warrant for highest accuracy, we employ Monte Carlo dose calculation for 6 MV beams, as implemented in 4D MC developed by Seco *et al* (2008). This code accounts for beam hardening and the tongue-and-groove effect by using first Compton scatter in the MLC medium. We extend the method to allow photon transport through the jaws and MLC using multiple Compton scatter.

Of the first studies using MC for IMRT optimization, Jeraj and Keall (1999) performed optimization on the MC-generated pencil beam (PB) using a narrow beam approach, where no treatment head scatter or transmission component is taken into account. The method predicted an initial backprojected IMRT fluence with Monte Carlo N-particle transport (Friesmeister 1997), from which the narrow beam MC PBs would be used for dose optimization. EGS4 Monte Carlo code (Nelson *et al* 1985) was then used to generate the required PB for optimization of all beams. However, MLC delivery constraints, head scatter

variations with field sizes and motion effects in the patient breathing or MLC delivery were not taken into account. In this work, we employ MC to generate the PB dose distributions for all the beamlets used in the optimization procedure and for six breathing phases. Therefore, these MC-generated PBs account correctly for not only heterogeneity effects in the lung region but also motion effects due to the patient breathing.

For this study, we developed the broad beam approach to generate Monte Carlo pencil beams (MCPB), instead of the narrow beam approach described in Jeraj and Keall (1999). The broad beam approach guarantees that the treatment head scatter and transmission contributions to the MCPB are accurately accounted for in the final dose. For each beam direction, the X and Y jaws are set such that the PTV is encompassed within the jaw opening plus a 1–2 cm margin to account for MLC delivery restrictions, penumbra and lateral scatter effects of the edge MCPBs. The MLCs are also placed such as to generate an identical field size as the jaw opening, guaranteeing an identical jaw and MLC field size. We then break up the open field into adjacent PB fluence squares, where all the particles within each PB fluence area are sampled to produce a MCPB dose. For example, a $10 \times 10 \text{ cm}^2$ field will have a total of 100 MCPBs each 1 cm^2 in area. This method guarantees that by combining all the MCPBs to generate a homogenous open field dose in water, we obtain the correct output factor for that open field generated by the jaws and MLC. In addition, it also guarantees that once an IMRT fluence map has been generated after optimization, very little or no re-normalization of this fluence map is required to account for head scatter and transmission effects caused by the leaf sequencing pattern.

3. Robust phase-adapted 4D-optimization model

In IMRT optimization, an otherwise optimal plan can turn out suboptimal in the delivery, if motion errors are encountered. We will elaborate on these possible outcomes in section 4.4. In the context of engineering design, there has been evidence illustrating that if errors are not taken into account during the design optimization, the actual phenomenon that the design aims to achieve can completely disappear (e.g. see Ben-Tal and Nemirovski (1998)). Recent works have been devoted to problems with convex objectives and constraints (e.g. linear). These works have shown that a convex optimization problem with parameter uncertainty can be transformed to another convex optimization problem (Ben-Tal and Nemirovski 1998; Bertsimas and Sim 2006). More recently, local search methods have been expanded to robust optimization of simulation-based problems. They entail finding descent directions and iteratively taking steps along these directions to optimize the robustness, i.e. reducing the worst-case cost in an unconstrained setting (Bertsimas *et al* 2010a) and in a constrained setting (Bertsimas *et al* 2010b).

Traditionally, robust optimization in the context of motion uncertainty in IMRT has been approached from a probabilistic point of view, where the errors were described as uncertainties in the probability density function of the breathing phases. Using a quadratic objective, the robust problem was posed either as a minimization of the expectation values (Unkelbach *et al* 2007) or via the robust counterpart formulation of a linear program (Bortfeld *et al* 2008).

In this study, we achieve robustness by taking all available information into account and providing a solution that is adaptive to the changes during treatment. More specifically, we take into account the CT data of all breathing cycles and solve a constrained spatiotemporal optimization problem. All anatomical volumes of interest are divided into volume elements, also called voxels. The dose deposited to each voxel i is computed using a linear model as

$$D_i(\mathbf{x}) = \sum_{j \in PB_i} d_{ij} x_j, \quad (1)$$

where d_{ij} is the respective 3D-dose influence matrix and x_j is a given beamlet intensity from the set of all beamlets PB. Since we seek to account for breathing effects as they occur in time, we compute the corresponding 4D dose components d_{ij}^p for each breathing phase p and rewrite the equation (1) for phase p as

$$D_i(\mathbf{x}) = \sum_{p \in \text{Phases}} \sum_{j \in PB_i} d_{ij}^p x_j^p. \quad (2)$$

Note that $\mathbf{x}$ is a vector of beamlet intensities x_j as elements, which depends on the phase p , i.e. $\mathbf{x} = ((x_1^1, \dots, x_j^1, \dots, x_{PB}^1), \dots, (x_1^p, \dots, x_j^p, \dots, x_{PB}^p), \dots, (x_1^P, \dots, x_j^P, \dots, x_{PB}^P))$. A quadratic objective function (Unkelbach *et al* 2007) is employed for the optimization, which is given by

$$E(\mathbf{x}) = \sum_{n \in \mathcal{V}} \frac{\alpha_n}{|V_n|} \sum_{i \in V_n} [D_i(\mathbf{x}) - D^{\text{pres}}]_+^2. \quad (3)$$

The operator $[\cdot]_+$ delivers the argument if the argument is positive definite and zero otherwise. Note that $\mathcal{V}$ denotes the set of all voxels, divided in volumes of interests V_n with the corresponding weights α_n . These weights are chosen accordingly to satisfy the clinical dose specifications. We will discuss the actual prescribed dose values for each clinical case we studied in section 4.

To determine a plan that is least sensitive to breathing motion and irregular breathing, we formulate the 4D-optimization problem as

$$\min_{\mathbf{x}} E(\mathbf{x}) \quad (4)$$

$$\text{subject to } \frac{|x_j^p - x_j^{(p+1) \bmod P}|}{\max(x_j^p, x_j^{(p+1) \bmod P})} \leq \Gamma, \quad p=1, 2, \dots, P \quad (5)$$

$$x_j^p \geq 0, \quad \forall j \in PB, \quad p=1, 2, \dots, P \quad (6)$$

through a minimization of the deviations between the delivered and prescribed dose.

Constraint (5) ensures that the intensities x_j^p are within delivery limitations, denoted by the scale Γ . Furthermore, a closed boundary condition is imposed via $p+1 = (p+1) \bmod P$ in constraint (5) to also ensure closeness of intensities for the last breathing phase to the first phase.

The scale Γ is a small positive number and can be determined by the actual delivery modus (e.g. sequencing limitations). The notion of Γ also offers a more generalized approach to the 4D-IMRT optimization. We can regard $\Gamma = 0$ as the static and $\Gamma = 1$ as the optimal tracking limit, as discussed in Trofimov *et al* (2005). In Nohadani and Bortfeld (2010), we showed that a value of $\Gamma = 5\%$ best captures the motion effects while remaining quasi-static and ensuring deliverability. We therefore chose this value for our lung cases to best exploit the 4D advantage. However, depending on the actual treatment modality and setting, this number may vary.

Note that in principle, one has to check whether the resulting intensities can be sequenced at all. Direct-aperture optimization techniques address this issue straightforwardly, as shown e.g. by Bergman *et al* (2006). Since a direct-aperture optimization is outside the scope of this study and a relatively smooth fluence map can be sequenced with negligible errors (as is the case here), it is justified to assume that the overall delivery limitation lies within the magnitude of intensity changes between the maps. Constraint (5) is imposed to cope with this limitation.

We have implemented this framework in C++ using object-oriented tools and in a fashion that enables us to compute the dose to an anatomic voxel and its gradient with respect to the beamlet intensities. Thus, we can conduct a gradient-based optimization, which is highly efficient and does not require the detailed knowledge of the uncertainty, as discussed by Martin *et al* (2007). Moreover, during each gradient-descent step, we adjust the step size in order to satisfy constraint (5). Since the step size is diminishing, the convergence criteria still hold.

Furthermore, the number of participating non-zero dose components in the 4D-optimization problem (4) grows with the number of beam directions as well as breathing phases considered. In order to adapt the computational complexity to the limitations of current commercial desktop computers, we down-sample the dose influence matrices d_{ij}^p by using the importance sampling method of Thieke *et al* (2002). Despite the data intensive MC dose calculation we conducted for all discussed clinical cases, it was possible to conduct the 4D-optimization for five to seven beam directions and six breathing phases on an Intel Xeon quad-core 1.86 MHz CPU with 4GB of RAM within 20 min for each patient. In the following, we present lung cancer cases for which we conducted the 4D-optimization, as introduced in this paper, in order to account for breathing motion during the treatment. For comparison, we also conducted the 3D-optimization as being conducted in conventional gating plans.

4. 3D-gating versus 4D-robust optimization

To measure the performance of the introduced 4D-optimization method, we compare the resulting plans of clinical lung cancer patients with the corresponding gating-based plans, as they were conducted at the Massachusetts General Hospital (MGH) on these patients. The gated window is optimized to incorporate the phases with the least motion variation and matches the clinically applied plan. In our analysis, we first compare the target coverage of these two methods. Next, we will elaborate on sparing of the healthy tissue and of the organs at risk (OAR). To measure the sensitivity as a means to measure the robustness of the final plans, we study the outcome of the optimized plans when delivered during irregular breathing periods of the patients, as it usually occurs in the clinical practice.

4.1. Target volume

Since the 4D-optimization method exploits the target motion in the planning stage, it is possible to omit those margins, which were added to compensate for this motion. For better

comparison, we describe in detail how the 3D-PTV is extracted and how we propose to determine the phase-adapted 4D-PTV. Figure 1 illustrates these margins. Assuming that the gross tumor volume (GTV) follows a hysteresis-shaped trajectory during the registered breathing phases, as shown in figure 1(a), the internal target volume (ITV) is marketed as a phase envelope of the target within the gating window, which is between 40% and 60%. This ITV is expanded by 5 mm to account for microscopical disease surrounding the target, resulting in the clinical target volume (CTV). A further margin of 10 mm is added to the CTV to account for setup and other random errors, resulting in the 3D-PTV, as shown in figure 1(b).

On the other hand, for the phase-adapted plan, we forego the ITV margins and obtain the CTV by adding the corresponding 5 mm margins to the GTV at 50% directly. To compensate for setup errors, we also add 10 mm margin and obtain the phase-adapted PTV, as shown in figure 1(c). Evidently, this PTV is then registered to all other phases and the robust plan is optimized with respect to all phases, as described above. These margins are the same for both patients and follow the clinical protocols at MGH. Note that while gating ‘freezes’ the motion through the ITV convolution, our method accounts for the variation in the location of the tumor through the phase-adapted 4D-optimization.

4.2. Target coverage

For the optimization methods, we follow the same dose constraints as practiced for lung cancer patients at MGH. The prescribed dose D^{pres} to CTV is 63 Gy for patient 1 and 45 Gy for patient 2. Figure 2 illustrates a dose–volume histogram comparison between a gated plan that was delivered to an optimized breathing window and a 4D-robust plan that was optimized based on the robust approach described in equation (4). The 4D-optimization method yields to a dose coverage to PTV that falls off sharper for higher doses and yet delivers the prescribed dose to the most parts of the PTV. In the gating-based optimized plan (dashed line of figure 2), we observe both more under- and over-dosed regions of PTV.

To quantify the differences, we measure D_{95} and D_{max} , which allows us to analyze the quality of the dose distribution. Note that a dose of at least D_x is received by $x\%$ of voxels and D_{max} denotes the maximum dose delivered. An alternative comparison provides the concept of equivalent uniform dose (EUD) which probes the clinical relevance of dose distribution. The underlying assumption is that the uniform distribution of the corresponding biological equivalent dose will lead to the same cell kill in the tumor as the actual non-uniform dose distribution. Following equation (1), we use the concept of generalized EUD (Niemierko 1999) to compute

$$\text{EUD}_n = \left(\frac{1}{N_n} \sum_{i \in V_n} D_i^{a_n} \right)^{1/a_n}. \quad (7)$$

Since the PTV is the volume of interest V_n , we chose the exponent $a_n = -10$ to emphasize higher dose values.

For patient 1, we measure an EUD of 62.8 Gy for the 4D-robust plan and 61.3 Gy for the gated plan. Similarly, we measure an EUD of 44.8 Gy for the 4D-robust plan and 44.1 Gy for the gated plan for patient 2. Table 1 presents these values. In both cases, the 4D-optimized plan delivers an improved dose distribution and coverage to the target volume. In fact, the deviation of the EUD from the prescribed becomes vanishingly small, when using the proposed 4D-optimization method, suggesting almost no under-dose to the PTV.

Furthermore, the long tail of the dose distribution, resulting in a very high maximum dose for the gated plan, is omitted in the 4D-robust plan. We truncated this region in figure 2 for visualization purposes, but added the value to table 1 to demonstrate that a non-robust approach can end up in extreme hot spots, when using gating in combination with high-precision Monte Carlo dose calculation. Using the 4D-robust approach allows us to distribute the necessary dose over all phases, hence a larger search space for the optimization, and obtain both an improved dose coverage as shown by the EUD analysis and better controlled maximum dose.

4.3. Healthy tissue sparing

One of the key advantages of our proposed approach is that it exploits the enlarged search space to provide a more robust plan that best spares all tissue from overdose during all breathing phases. This is pronounced particularly in the lungs as well as in other OAR. We compute the mean lung dose (MLD) to the combined lungs, i.e. the union of the left and the right lung. In general, the MLD should not exceed 27 Gy (Vanderstraeten *et al* 2006). Table 2 illustrates that this MLD constraint for both patients is well satisfied using gating or the 4D-robust method. Nevertheless, we observe a lower MLD for both patients in the 4D-robust plan.

Table 2 also contains V_{20} and V_{30} for both patients. Note that V_x denotes the relative lung volume (in percentage) that receives at least x Gy. The protocol at MGH requires that $V_{20} \leq 35\%$ and $V_{30} \leq 20\%$. For patient 1, we observe small violations of V_{20} and V_{30} in the gating case which is primary due to the trade-off between achieving the prescribed dose to PTV and sparing the lungs. Our results demonstrate a significant reduction of V_{20} and V_{30} for patient 1 and a small reduction of both measures for patient 2 using the 4D-robust method, demonstrating the advantages of the 4D optimization method also with respect to lung sparing. Figure 2(a) also shows the overall improvement in lung sparing for patient 1 with the larger amplitude of motion and, thus, more difficult lung sparing.

The dose distribution to the OAR is shown in table 3. We compare the maximum doses to the esophagus $D_{\text{Esoph}}^{\text{max}}$, to the heart $D_{\text{Heart}}^{\text{max}}$ and to the spinal cord $D_{\text{S.Cord}}^{\text{max}}$. The clinical protocols at MGH for these constraints are $D_{\text{Esoph}}^{\text{max}} \leq 55$ Gy, $D_{\text{Heart}}^{\text{max}} \leq 45$ Gy and $D_{\text{S.Cord}}^{\text{max}} \leq 40$ Gy. We observe that both methods do not violate the dose constraints to the heart and to the spinal cord for both patients. The violation for $D_{\text{Esoph}}^{\text{max}}$ for patient 1 is due to the large size of the tumor and its proximity to large parts of the esophagus. While there is a violation of the order of 3% for the gated plan, the $D_{\text{Esoph}}^{\text{max}}$ for the 4D-robust plan is clearly under the thresholds. Overall, we observe a lower maximum dose to all three OARs when using the proposed 4D method for both patients, supporting the improved dose distribution.

In comparison, we observe better results for patient 1 than patient 2. This is because the PTV of patient 1 is smaller, closer to OARs and has a more challenging geometrical shape than in patient 2. Moreover, the amplitude of the respiratory motion for patient 1 was greater than that for patient 2, making the issue of robustness more relevant. In all measures, the results of the 4D-optimization are at least as good as gating, and for most measures even significantly improved (see over-dose) at a comparable computational expense. We also conclude that the enlarged search space in the 4D-robust method also warrants for an overall better normal tissue and OAR sparing.

4.4. Worst-case performance

As mentioned, gating is sensitive to the breathing window, during which the radiation is delivered (Trofimov *et al* 2005). We employ Monte Carlo dose calculations, in order to

avoid possible dosimetric errors dominating window sensitivities. In general, since the planning and imaging occur prior to the treatment and not simultaneously, the assumed window for gating may not coincide with the actual current breathing phase. To measure potential worst-case outcomes, we investigate the effect of irregular breathing during the treatment. In patients with lung cancer, this usually results in the elongation of the current breathing phase and shortening of the following phase. We study this effect by computing the dose that is delivered when the breathing pattern becomes irregular, i.e. when the optimized intensities $\mathbf{x}^{p^*}$ for the chosen gating window p^* are delivered at a later phase $p^* + 1$, according to

$$D_i^{\text{irregular}}(\mathbf{x}^{p^*}) = \sum_{j \in PB_i} d_{ij}^{p^*+1} x_j^{p^*}. \quad (8)$$

To demonstrate a potential worst-case outcome, figure 3 illustrates the DVH for both patients when gated at the optimal window (as shown in figure 2) as well as when gated while the patient is breathing irregularly. Due to the smaller PTV as well as the larger amplitude of motion in patient 1, we observe a significant degradation of the DVH for and an unacceptable under-dose to the PTV, as shown in figure 3(a). These deviations are smaller for patient 2, as shown in figure 3(b) due to the reduced motion, thus less separation between the phases. We will elaborate these discrepancies later, using counterplots of the actual dose distributions.

In comparison, we also measure the sensitivity of the 4D-robust plan during irregular breathing. This is modeled by extending one of phases in time such that it covers the following phase. In order to determine the worst-case outcome, we calculated this scenario for all six phases, during which the patient may breath irregularly and, thus, that phase is lengthened into the following phase. All six scenarios are compared and the worst case, defined as the plan whose DVH for PTV deviates most from the non-perturbed 4D-robust DVH, is determined. This is shown in figure 3 as well. We observe practically no deviations, underlining that the 4D-robust plan is in fact not sensitive to irregular breathing during all phases of the treatment. This robustness is achieved through the optimization algorithm and enforced particularly by constraint (5), which ensures that beam intensities of different phases are close to each other. Therefore, the method intrinsically accounts for potential effects of mismatch of phases and, thus, irregular breathing. It is obvious that these effects are negligible, if the amplitude of motion is small, as is the case for patient 2, shown in figure 3(b). But it is remarkable that for patients with large amplitudes of motion, as patient 1, the robust 4D-optimization method delivers a non-sensitive plan against irregular breathing, while the gating vastly degrades, as shown in figure 3(a).

To best follow the difference between these two planning methods as well as demonstrate the sensitivity to irregular breathing, figure 4 illustrates the dose distribution for patient 1. First, we observe that the gated plan degrades, when delivered during irregular breathing, in particular for patient 1, i.e. when we compare the two distributions in the top row of figure 4. We note that the anterior part of the target is barely irradiated, when gated during irregular breathing. This is evidently due to the displacement of the tumor that occurs between the phases p and $p + 1$. To assess the magnitude of this inter-phase motion, we compare five distinguishable points in the upper part of the tumor within these neighboring phases and conclude that the vector between these two phases for this part of the tumor has an average Euclidean length of 7.9 ± 1 mm (not shown here). Note that these values may be in part contaminated by errors from the deformable registration, as pointed out in section 2.1. Nevertheless, this large displacement of the target explains the vast degradation of the

dose distribution, as shown for the target in the DVH of figure 3(a). On the other hand, for patient 2, we measure an average displacement of 1.2 ± 1 mm, which explains the marginal degrading observed in figure 3(b).

For the 4D-optimized plans, we observe an improved dose coverage to the target, when compared to the gated plan for both patients. For both patients, we also observe a reduction in the hot spots, in particular in patient 1, corresponding to the results of table 1.

On the other hand, one may use $\Gamma = 0$ in constraint (5) and obtain a set of influence maps that are invariant to phase changes. By our definition of the worst-case test, i.e. when irregular breathing occurs and the phases are shifted, the outcome of these static fluence intensities is immune to any shift and, thus, maximally robust. However, this static solution is nominally suboptimal and requires enlarged margins leading to increased dose to OARs and, thus, clinically not relevant, as discussed in Nohadani and Bortfeld (2010). Therefore, to demonstrate robustness, we compare the phase-adapted 4D-method to standard practice in the clinic, i.e. gating and expose both to irregular breathing.

5. Discussion

Once a treatment plan is optimized, the resulting fluence maps need to be sequenced in order for the planned dose to be delivered to the patient. Another source of error, however, occurs during the sequencing process. When the optimized dose delivery is compared to the deposited dose after the sequencing using Monte Carlo dose calculation, an error of up to 5% has been reported (Cui *et al* 2008). These errors depend on the number of sequencing segments and can be superposed by the motion uncertainties. However, our 4D-optimization technique delivers beamlet intensities that are Γ -close to each other. This advantage suggests that this method can reduce the total number of required sequenced segments. A reduction of the number of fluence segments will limit the sequencing errors to a minimum. Therefore, our proposed method has the potential to be inherently robust against sequencing errors as well. A quantitative demonstration for this advantage requires the incorporation of an actual sequencing algorithm. However, these algorithms have their own subtleties. When analyzing the quality of the final results, it is not possible to clearly disintegrate and attribute the features to either the robust method or the sequencing algorithm. We, therefore, concentrate on the robust method and will follow up on further connections later.

It is noteworthy to point out that a reduction in the number of segments increases the delivery efficiency, which is typically defined as the ratio of planned dose (in cGy) to the monitor units (in MU). From clinical practice at MGH, an IMRT plan requires 25–40 segments for each beam direction. This leads to an average efficiency of ~ 0.25 cGy MU⁻¹ for a sizable number of patients. In the limit of one segment per beam, which resembles the 3D unwedged conformal radiation therapy, we obtain an average efficiency of ~ 0.90 cGy MU⁻¹ for the same number of patients. Since our proposed method will provide quasi-static plans and, thus, potentially a lot less segments, we can assume that it can improve the delivery efficiency significantly. In this paper, we assume that the 4D CT scan represents the extent of the motion fully. We do consider variations of the duration of the different breathing phases but not variations in the spatial location of the phases. The latter would have to be taken into account with margins or with robust optimization (Chan *et al* 2006), or possibly with adaptive planning strategies, which are beyond the scope of this paper. In other words, we consider motion but only to a limited degree the uncertainties of the motion.

6. Conclusion

In conclusion, our approach takes time effects into account and provides a 4D-optimized IMRT plan that is inherently robust against motion, irregular breathing, sequencing and delivery uncertainty. This spatiotemporal optimization also allows us to reduce margins due to improved dose coverage. It takes into account all breathing phases and provides a quasi-static plan, and thus improves the delivery efficiency. Moreover, we employ Monte Carlo dose calculation to warrant the highest dosimetric accuracy, as is pertinent for a study of motion effect in lung cancer.

In comparison with conventional gating techniques, we show that for two clinical lung cancer cases representing a large spectrum of cases, the presented phase-adapted 4D-optimization delivers results that are by all measures at least as good as gating, and in one case with large magnitude of motion considerably better at a comparable computational expense. For large moving targets, the advantages both in terms of target coverage and OAR sparing are significant. A sensitivity test shows that if an otherwise optimal gating plan is delivered during irregular breathing, the outcome is sufficiently degraded to be clinically dismissible. In contrast, we demonstrate that if the phase-adapted 4D-optimized plan is delivered during such an irregular breathing pattern, owing to its quasi-static beam intensities, the outcome is almost identical to the unperturbed dose distribution, thus least sensitive to uncertainties. Furthermore, we discuss that using the proposed method will notably improve the delivery efficiency. While the current results act as a proof of concept, we plan to expand our study to a larger number of cases.

We also wish to emphasize that the delivery of a gating-based plan takes substantially more time than the proposed quasi-static plan, which can be delivered throughout all breathing phases. This feature equips this method to be a strong candidate for single-arc approaches which reduce the delivery time down to one single rotation of the gantry. We believe that an extension of this method can exploit the motion and the additional degrees of freedom to optimally deliver the dose in a minimal duration.

Acknowledgments

We would like to thank N Choi for providing the lung patient data. We are also very grateful to H Paganetti for providing some of the computational resources. This work was supported by the National Cancer Institute of the United States under grants R01-CA118200 and R01-CA103904.

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Figure 1.

Graphical representation of the target volume through the registered phases of breathing: (a) a sketch of the positions along a hysteresis-shaped breathing cycle; (b) margins for irradiation within the gating window and (c) margins for the phase-adapted planning, shown as an example for the 50% phase.

Figure 2.

Dose-volume histogram: optimized IMRT plan based on Monte Carlo dose calculation, when all six breathing phases are considered (4D-robust) and when the dose is applied only to one phase (gating) for (a) a patient with smaller PTV and large amplitude of motion and (b) a patient with a large PTV and small displacement.

Figure 3.

Dose-volume histogram: worst-case comparison for an optimized IMRT plan based on Monte Carlo dose calculation, when all six breathing phases are considered (4D-robust solution) and when the dose is applied only to one phase (gating). The optimal beam intensities are applied to dose cubes that are shifted by one phase when the breathing is irregular. (a) A patient with a very large amplitude of motion and (b) a patient with a small PTV displacement.

Figure 4.

Dose distributions for patient 1. The shaded region (green) marks the target. The contour lines are for 20%, 50%, 95% and 105% of the prescribed dose. First row: the dose for the optimal gated plan delivered to the optimal gating window (left) and the optimal gated plan, delivered during irregular breathing (right). Second row: the 4D-optimized quasi-static plan, delivered to all phases (left) and 4D-optimized plan, delivered during irregular breathing (right).

Table 1

Target coverage for both patients. The prescribed dose D_{pres} to PTV is 63 Gy for patient 1 and 45 Gy for patient 2.

Method	Patient 1			Patient 2		
	D_{pres} -EUD (%)	D_{95}	D_{max}	D_{pres} -EUD (%)	D_{95}	D_{max}
Gating	1.2 Gy (2%)	57.1 Gy	72.3 Gy	0.9 Gy (2%)	41 Gy	50.8 Gy
4D-robust	0.2 Gy (0.3%)	59.5 Gy	68.6 Gy	0.2 Gy (0.4%)	41.9 Gy	49.0 Gy

Comparison for lung sparing (combined left and right lungs) using 3D-gating based and 4D-robust methods for both patients. The protocol at MGH requires $MLD \leq 27$ Gy, $V_{20} \leq 35\%$ and $V_{30} \leq 20\%$.

Table 2

Method	Patient 1			Patient 2		
	MLD	V_{20}	V_{30}	MLD	V_{20}	V_{30}
Gating	16.6 Gy	35.5%	21.6%	12.9 Gy	24.4%	7.0%
4D-robust	6.7 Gy	8.6%	3.6%	12.1 Gy	22.6%	6.2%

Table 3

Comparison for OAR sparing using 3D-gating and 4D-robust methods for both patients. The constraints are $D_{\text{Esoph}}^{\text{max}} \leq 55 \text{ Gy}$, $D_{\text{Heart}}^{\text{max}} \leq 45 \text{ Gy}$ and $D_{\text{SCord}}^{\text{max}} \leq 40 \text{ Gy}$.

Method	Patient 1			Patient 2		
	$D_{\text{Esoph}}^{\text{max}}$	$D_{\text{Heart}}^{\text{max}}$	$D_{\text{SCord}}^{\text{max}}$	$D_{\text{Esoph}}^{\text{max}}$	$D_{\text{Heart}}^{\text{max}}$	$D_{\text{SCord}}^{\text{max}}$
Gating	56.6 Gy	44.9 Gy	40 Gy	43.1 Gy	28.6 Gy	35.5 Gy
4D-robust	31.5 Gy	30.3 Gy	25.8 Gy	42.2 Gy	27.7 Gy	34.1 Gy