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Technical Note

Comprehensive 4D robustness evaluation for pencil beam scanned proton plans

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ABSTRACT

Due to anticipated clinical benefits, moving targets are potential future indications for pencil beam scanned proton therapy (PBS-PT). However, currently they are not widely treated at PBS-PT facilities due to dosimetric uncertainties caused by motion. We developed a method, the 4D robustness evaluation method (4DREM), to realistically and efficiently assess all possible events impacting PBS-PT treatments in the thorax. Using the 4DREM in large cohorts of lung and oesophageal cancer patients, it will become possible to illustrate, in clinical practice, how to trigger robustness settings for plan optimisation and to select and apply motion mitigation techniques.

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Compared to conventional radiotherapy, pencil beam scanned proton therapy (PBS-PT) has demonstrated considerable clinical benefit for numerous tumour sites [1]. The high conformity achievable with PBS-PT allows higher tumour dose delivery (improving local control) and lower dose to adjacent healthy tissue, due to a lower integral dose [2]. These benefits of PBS-PT are extremely important for the treatment of moving targets, such as thoracic cancers (4D treatments), due to the critical structures surrounding the tumour (healthy lung and oesophagus tissue, heart, and spinal cord). Therefore, despite the fact that 4D PBS-PT is not currently widely used, moving targets are increasingly being considered for the near future at dedicated proton facilities.

Due to the finite range of protons and their sensitivity to variations in water equivalent thickness, the robustness of PBS-PT treatment plans may be compromised by small changes to the planning situation [3]. To a small extent, machine errors occurring during the treatment delivery (influencing spot position, delivered monitor units per spot, spot energy, and absolute time point of spot delivery) can result in deviations in the delivered dose from the clinical planned dose distribution, which has been calculated by the treatment planning system (TPS) and approved by the radiation oncologist. Moreover, deviation in the patient treatment position from the planned position can have a pronounced

dosimetric impact. Finally, anatomical variations within the patient throughout the treatment course may result in density variations along the proton beam path, which can cause range errors. Particularly for thoracic treatment sites, motion due to respiration can disturb the planned dose distribution on delivery.

Despite the presence of respiratory motion, treatment planning is performed on a snapshot representation of the patient, resulting in differences between the planned and delivered dose distribution. For PBS-PT in the thorax region especially, dose inhomogeneities may arise within the target due to the interference of the time structure of delivery and target motion due to the patient's respiration pattern (interplay effects) [4].

Previous studies have analysed and reported the robustness of PBS-PT plans to setup and range errors for non-moving targets [5–10]. Regarding PBS-PT for moving targets, Knopf et al. [11] exhaustively assessed the impact of interplay effects on planned dose distributions for liver tumours by including the timeline of the delivery in the TPS process. With the aim of comparing different optimisation strategies, Liu et al. [12] examined the combined influence of setup and range uncertainties and respiratory motion on lung cancer intensity-modulated proton therapy (IMPT) plans. Robustness evaluation studies on mediastinal lymphoma patient cases (against inter- and intra-fractional uncertainties and interplay effects) were performed by Zeng et al. [13,14]. Lin et al. [15] investigated the effect of motion, range errors, and patient setup variations in a treatment-planning comparison study. They compared double scattering and single-field uniform dose (SFUD)

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proton therapy for stage III locally advanced non-small cell lung cancer (NSCLC) patients. However, in this study the impact of machine errors and interplay was not evaluated in combination with the other afore mentioned effects. Finally, Inoue et al. [16] developed a method to evaluate robust optimised IMPT plans for stage III NSCLC patients. This robustness evaluation tool considered the impact of setup and range errors, breathing motion, and interplay. However, the impact of the combination of interplay with setup and range errors, or the machine errors, was not incorporated. Furthermore, only the interplay per energy layer and not per spot, was considered. Other more recent studies also evaluated the robustness of different types of lung cancer IMPT treatment plans to setup and range uncertainties, and separately, breathing motion and interplay effects [17,18].

This study arose as a follow-up of the publication by Inoue et al. [16], and so in this technical note we report on the development and application of a more comprehensive and refined tool. With our new 4D robustness evaluation method (4DREM), it is now possible to assess the impact of all the above-mentioned PBS-PT effects simultaneously. The 4DREM is essential to safely extend PBS-PT to thoracic indications. It allows the assessment of full PBS-PT treatment courses for moving targets, helping to define an optimal clinical protocol for this group of patients.

Materials and methods

Effects of 4D PBS-PT

Our 4DREM was implemented using in-house developed Python scripts, through features available in the RayStation TPS (RaySearch Laboratories, Stockholm, Sweden). Setup and range errors were simulated using representative values from literature [10]. Furthermore, potential machine errors, anatomy changes, breathing motion, and interplay effects occurring during treatment delivery were considered based on treatment-plan specific delivery-machine log files and 4DCT imaging data (see Fig. 1A).

Setup and range errors

Fourteen scenario dose distributions (representing 14 possible full treatment courses) were simulated. For each scenario, eight fractions were taken into account [15]. The accumulated setup error effect on the dose for a fractionated treatment was simulated by defining a systematic and random (day-to-day) fraction of this error. In particular, systematic setup errors were simulated by shifting the planning isocentre in 14 different x, y, and z directions (vertices and faces of a cube). The fractionation effect was considered by randomly picking, for each fraction per scenario, an additional isocentre translation by sampling a normal distribution. Range errors were simulated by randomly applying a perturbation of 0 or ± 3 % on the CT densities [19]. Due to the systematic nature of range uncertainty, for all fractions of the same scenario, the same range error was considered [20].

Machine errors, anatomy changes, breathing motion, and interplay effects

From dry run deliveries of the calculated dose distributions, machine log files were obtained. The nominal plan was split into sub-plans using a dedicated script that retrieves information from the delivery log files (spot position, dose, and energy and the absolute time of delivery). Subsequently, machine errors, anatomy changes, breathing motion, and interplay effects were simultaneously included by calculating sub-plan dose distributions on particular 4DCT phases. The 4D dose was accumulated on the planning 4DCT as well as on repeated 4DCTs (acquired in successive weeks during the course of radiotherapy). To split the delivery into sub-plans, a constant breathing cycle of 5 s was assumed [21].

The 4D dose accumulation in each of the available 4DCTs was performed by warping the sub-plan dose distributions per phase onto the end-of-exhalation planning CT phase. The warped doses were subsequently summed together. The deformable image registration (DIR) algorithm used for the dose warping (and contour propagation), called ANACONDA (Anatomically Constrained Deformation Algorithm), is included in the TPS [22]. For all DIRs, the delineated clinical target volumes (CTVs) were used as controlling regions of interest (ROIs). This ensured that the alignment of these contours in the registered image pairs drove the deformation [23].

Combination − 4D robustness evaluation method (4DREM)

The 4DREM makes it possible to combine the evaluation of setup and range errors with machine errors, anatomy changes, breathing motion, and interplay effects. For this study, a dose distribution was calculated per sub-plan, on a particular phase of a particular 4DCT set, considering setup and range errors. A fraction dose was calculated by applying the same setup and range errors to all sub-plan doses of the specific 4DCT and summing the phase-specific contributions. For each fraction calculation, the 4DCT starting phase of the delivery was randomly selected. Finally, the entire treatment course dose distribution was obtained by performing dose accumulation of several fraction doses based on different 4DCTs. In total, 14 4D accumulated scenario doses were obtained, each representing a possible treatment course of a particular nominal plan (Fig. 1A).

Application to patient data

IMPT plans using five times layered rescanning for a sample lung cancer patient (NSCLC stage III) and a sample oesophageal cancer patient were created in RayStation version 6.99 using the Monte Carlo dose engine. Both patients had previously been treated at the UMCG with conventional photon radiotherapy.

The minimax robust optimisation approach was used, aiming for robustness against ± 3 % range uncertainties and setup uncertainties between 5.0 mm and 7.5 mm [19]. For both sample patients, a 3D robust optimised plan (created on the averaged planning CT) and a 4D robust optimised plan (created on the end-of-exhalation planning CT phase) were generated. For the 4D robust plan, all planning 4DCT phases were used during the optimisation [24]. Three beam directions were used for both 3D and 4D robust optimised plans for the NSCLC case (one left-posterior oblique and two right-posterior oblique fields). For the oesophagus case, two beam directions (posterior–anterior and right-posterior oblique) were chosen. A nominal dose was prescribed in terms of relative biological effectiveness (RBE), 60.00 Gy_{RBE} in 25 fractions (lung case) and 41.40 Gy_{RBE} in 23 fractions (oesophagus case) to the internal clinical target volume (iCTV) in the 3D robust optimisation and to the CTV in the 4D robust optimisation. For each patient, to ensure a fair plan comparison, the difference in fulfilled median dose to the target (prescribed structure) between 3D and 4D plans, was within 0.5 Gy. A density override to muscle tissue (1.050 g/cm^3) was applied within the iCTV for the 3D robust optimisation. For the oesophagus case, the feeding tube and contrast were also delineated and an override applied of the same mass density value as muscle tissue.

All nominal plans created were visually inspected by physicians and medical physicists (regarding beam arrangements, overrides, adequate target coverage, and minimisation of organs-at-risk [OARs] dose). Preliminary robustness evaluation was then performed on the averaged planning CT towards setup and range errors alone. If target coverage in the minimum dose per voxel over all scenarios (voxel-wise worst-case [minimum] dose distribution) was acceptable (D_{98}(iCTV) $\geq$ 95 % of prescribed dose), the plans

Parameters for one full treatment evaluation

A

Voxel-wise worst-case dose

B.I

DVHs target and OARs
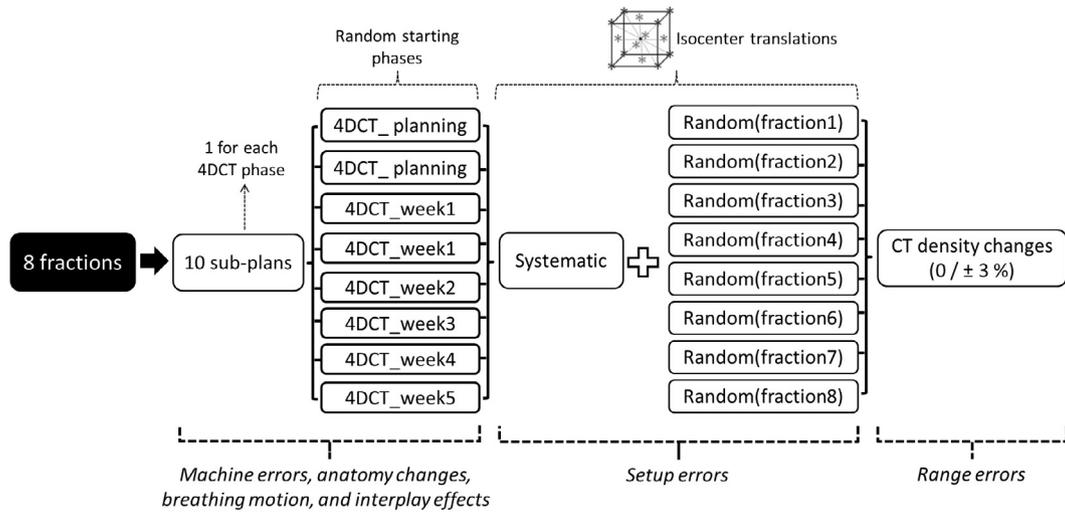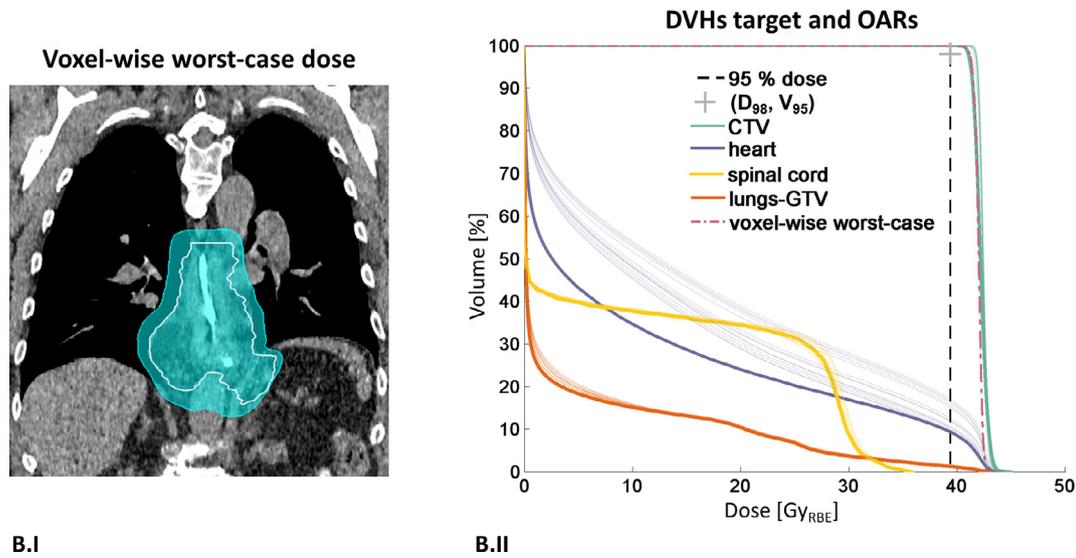
B.II

Fig. 1. A: Schematic representation of a treatment scenario simulated through the 4DREM for PBS-PT. **B:** Application results of the 4DREM in the 4D robust optimised IMPT plan created for the sample oesophageal cancer patient. **B.I:** Voxel-wise worst-case (minimum) dose distribution resultant from the inclusion of the combined 4D PBS-PT disturbing effects. In white is the delineated CTV and the light blue line shows the 95 % isodose. **B.II:** Heart, spinal cord, lungs-GTV, and CTV DVH curves for the nominal plan and all 14 simulated treatment scenarios (in the same coloured transparent lines), and resultant DVH(CTV) for the voxel-wise worst-case (minimum).

were delivered in dry runs at our proton facility to obtain log files. The in-air spot sigma at our beam line ranges from 6.5 mm to 3.0 mm for proton energies from 70 MeV to 230 MeV.

For both patients, a planning 4DCT and five weekly repeated 4DCT scans (each with ten phases) were available. The iCTVs were delineated on the averaged planning CT (volumes of 153.2 cm^3 and 399.7 cm^3 for the lung and oesophageal cancer patients, respectively), taking into account all breathing phases. Gross tumour volumes (GTVs) and CTVs were defined on all image phases by contour propagation and subsequent correction by an experienced physician. Motion amplitudes were given by the mean of all the deformation vector lengths within the CTV resulting from DIR between the end-of-exhalation and end-of-inhalation phases of a particular 4DCT [16]. Averaged over all six 4DCTs, the motion amplitudes were 4.0 ± 0.8 mm (lung case) and 6.5 ± 0.9 mm (oesophagus case).

Sub-plans (derived from the delivery log files) and all available 4DCT scans were used to evaluate the treatment plans by the 4DREM. The available 4DCTs were distributed and equally weighted through the eight evaluated fractions. For the first two fractions, 4D dose accumulation of sub-plan doses was performed on the planning 4DCT, for the subsequent two fractions the first repeated 4DCT was used, and for the last four fractions the remaining repeated 4DCTs were successively selected (Fig. 1A).

Plan robustness to the combined disturbing effects was evaluated by the 4DREM on the end-of-exhalation planning CT phase through the voxel-wise worst-case dose distribution (obtained from the 14 scenario doses) [25,26]. The dose–volume histogram (DVH) of the CTV and respective metrics (V_{95} and homogeneity index [D_2-D_{98}]) were examined in the voxel-wise worst-case dose distribution. The voxel-wise worst-case dose was computed as the maximum dose per voxel over all scenarios (voxel-wise worst-case [maximum]) for D_2, and for V_{95} and D_{98} as the minimum. Additionally, the OAR DVH indices D_{mean}(heart), D_1(spinal cord), and D_{mean}(lungs-GTV) were averaged over all scenarios resulting from the execution of the 4DREM, and extracted for all plans.

Robustness evaluation for 4D PBS-PT

Results

The voxel-wise worst-case dose distributions obtained from the 4DREM were used to assess the robustness of 3D and 4D robust optimised IMPT treatment plans of a lung and an oesophageal cancer patients. Robustness was calculated for the combination of the disturbing effects expected when treating moving targets with PBS-PT. For the oesophagus 4D plan, we computed the DVHs of CTV, heart, spinal cord, and lungs-GTV for the nominal case and all treatment scenarios resulting from the 4DREM, and the corresponding voxel-wise worst-case dose (Fig. 1B). Small differences between nominal and voxel-wise worst-case dose distributions were observed for the 3D and 4D robust optimised plans for both sample patients (Table 1).

Discussion

Our 4DREM allows for the assessment of the robustness of PBS-PT plans by simulating setup and range errors in combination with machine errors, anatomy changes, breathing motion, and interplay effects. Compared to previous work, our method presents a more comprehensive, and hence more representative, evaluation [11–18]. Furthermore, the most recent Monte Carlo dose engine of the TPS was used instead of the less accurate Pencil Beam algorithm, the latter which over-predicts the dose delivered to the target for proton dose calculations in lung [27].

The influence of DIR motion estimation uncertainties on the dose accumulation of the 4DREM is rather limited. The selected DIR method (ANACONDA) was validated geometrically and dosimetrically in a previous collaboration study from our group for liver cases [28]. In this work the use of controlling ROIs in the application of DIR provided improved results. Therefore, for the 4DREM, the CTV is used as controlling ROI in order to improve accuracy around that targeted area. Additionally, multiple-field treatment plans and five times layered rescanning were used, which in our previous paper demonstrated to mitigate the DIR induced dosimetric errors for 4D PBS-PT.

The impact of fractionation is incorporated in the 4DREM by the simulation of a random setup error, dose accumulation performed in different 4DCTs, and de-synchronisation of the starting phase from fraction-to-fraction. By including the fractionation effect, the smoothening out of the dose over the treatment course is taken into account. Eight evaluated fractions (instead of the clinical delivery in 25 lung and 23 oesophageal radiotherapy fractions) were considered in order to reduce computation time. It has been shown that limiting the fraction number to eight is representative of the fraction-smearing effect of inhomogeneities in the target dose distribution for NSCLC PBS-PT [15].

Six 4DCTs were available for both sample patients (a planning 4DCT and five repeated 4DCTs). Considering that multiple 4DCTs

in the 4DREM already partially takes into account patient interfractional setup errors, only the remaining setup uncertainty needed to be added. Therefore, the proton isocentre vs. imaging isocentre accuracy, the patient re-positioning error, and the intra-fractional variability of patient bony anatomy (as quantified by Sonke et al. [29] for lung tumours using 4D cone beam CT scans) were estimated. The result was 2 mm remaining setup uncertainty, which was incorporated in the 4DREM in the simulated setup shifts. These shifts were calculated by scaling the systematic and random errors as in the treatment margin recipe provided by van Herk et al. [30].

Hoffmann et al. [31] demonstrated that large anatomical changes can lead to target under-dosage in IMPT of advanced lung cancer. Inter-fractional variability was included in this study through multiple 4DCTs. However, one should not forget the intrinsic limitations of 4DCT reconstruction. By considering an average breathing cycle, and neglecting any irregularity of the breathing pattern within one fraction, the accuracy of 4D dose calculations can be compromised. Furthermore, the number of different 4DCTs taken into account can have an influence on the 4DREM results. Future work will exploit the inclusion of more 4D information throughout radiotherapy, especially modelling intra-fractional motion, which could be extracted from CBCT images, camera-based systems or, in the future, from non-additional imaging dose techniques such as 4DMRI [32].

In this technical note we present results of the 4DREM application for two representative patients with intra-thoracic tumours, who could be future candidates to be treated at our proton facility. As a proof-of-concept, we have shown that both the planning protocol and subsequent delivery of 3D and 4D PBS-PT plans were clinically suitable; the 4DREM did not reveal any robustness shortcomings. This means that the optimisation parameters used and/or the application of rescanning as a motion mitigation technique were effective strategies for these patients. However, the question remains whether the applied optimisation/motion mitigation might have resulted in an overly conservative plan. The next step will include a larger patient cohort study with 20 patients (ten lung and ten oesophagus cases) with extensive numbers of repeated 4DCT datasets. This will allow for general conclusions concerning the impact of the disturbing effects of PBS-PT in the treatment of moving targets. In previous studies, 4D robust optimisation produced more robust and interplay-effect-resistant plans for targets of NSCLC cases than 3D optimisation [24]. Since the use of 4D robust optimisation implies more manual work and optimisation time within clinical workflow, we hope to estimate the benefits of this complex process in terms of plan robustness for a more representative number of cases, and to be able to generate a patient selection tool that can identify the need for 3D vs. 4D robust optimisation.

The great potential benefit of PBS-PT is the high conformity (allowing high doses to the tumour while sparing surrounding tis-

Table 1

Extracted nominal, scenarios, and voxel-wise worst-case dose distribution statistics for the 3D and 4D robust optimised plans of the sample NSCLC and oesophageal cancer patients.

Sample patient	Plan	Dose statistics									
		OARs						Target			
		D_{mean}(heart) [Gy$_{RBE}$]		D_1(spinal cord) [Gy$_{RBE}$]		D_{mean}(lungs-GTV) [Gy$_{RBE}$]		V_{95}([i]CTV) [%]		D_2-D_{98}([i]CTV) [Gy$_{RBE}$]	
		Nominal	Scenarios (mean ± SD)	Nominal	Scenarios (mean ± SD)	Nominal	Scenarios (mean ± SD)	Nominal	Voxel-wise worst-case	Nominal	Voxel-wise worst-case
Lung	3D	4.65	5.90 ± 0.36	39.93	39.44 ± 2.35	9.40	9.83 ± 0.20	99.98	100.00	3.61	2.92
	4D	2.52	3.10 ± 0.28	31.61	38.02 ± 3.02	10.47	10.68 ± 0.16	99.89	100.00	3.84	3.90
Oesophagus	3D	11.28	14.45 ± 1.44	31.13	31.39 ± 0.22	4.30	4.35 ± 0.06	100.00	99.60	2.24	3.14
	4D	10.96	15.01 ± 1.36	33.91	33.95 ± 0.13	4.28	4.53 ± 0.06	100.00	99.99	2.35	2.55

Abbreviations: 3D = 3D robust optimised plan; 4D = 4D robust optimised plan; D_2-D_{98} = homogeneity index.

sue). However, this feature of PBS-PT brings challenges for moving targets, requiring a high degree of treatment plan robustness. Therefore, comprehensive evaluation methods, such as the 4DREM for thoracic lesions treated with PBS-PT, enable:

- The establishment of an optimal clinical protocol, when used for subsequent treatment plan comparison studies. This allows the selection of optimisation strategies and helps to determine the need for additional motion mitigation techniques.
- Treatment planning confidence by testing plan robustness, which can eventually increase the number of proton centres performing these treatments in the future.
- Patient-specific quality assessment of future 4D adaptive workflows.

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Conflicts of interest statement

We have no conflicts of interest to disclose.

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