

Assessing dose rate distributions in VMAT plans

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Abstract. Dose rate is an essential factor in radiobiology. As modern radiotherapy delivery techniques such as Volumetric Modulated Arc Therapy (VMAT) introduce dynamic modulation of the dose rate, it is important to assess the changes in dose rate. Both the rate of monitor units per minute (MU rate) and collimation are varied over the course of a fraction, leading to different dose rates in every voxel of the calculation volume at any point in time during dose delivery.

Given the radiotherapy plan and machine specific limitations, a VMAT treatment plan can be split into arc sectors between DICOM Control Points of constant and known MU rate. By calculating dose distributions in each of these arc sectors independently and multiplying it with the MU rate, the dose rate in every single voxel at every time point during the fraction can be calculated. Independently calculated and then summed dose distributions per arc sector were compared to the whole arc dose calculation for validation. Dose measurements and video analysis were performed to validate the calculated datasets. A clinical head and neck, cranial and liver case were analyzed using the tool developed.

Measurement validation of synthetic test cases showed linac agreement to precalculated arc sector times within ± 0.4 s and doses ± 0.1 MU (one standard deviation). Two methods for visualization of dose rate datasets were developed: The first method plots a 2D histogram of the number of voxels receiving a given dose rate over the course of the arc treatment delivery. In similarity to treatment planning system display of dose, the second method displays dose rate as color wash on top of the corresponding CT image, allowing the user to scroll through the variation over time. Examining clinical cases showed dose rates spread over a continuous spectrum, with mean dose rates hardly exceeding 100 cGy/min for conventional fractionation. A tool to analyze dose rate distributions in VMAT plans with sub-second accuracy was successfully developed and validated. Dose rates encountered in clinical VMAT test cases show a continuous spectrum with a mean less than or near 100 cGy/min for conventional fractionation.

1 **1. Introduction**

2 The main quantity for radiotherapy efficacy is deposited energy per unit mass, measured in
3 units of Gray. Cell kill in vitro and tumor response in patients have clearly been shown to be linked to
4 the dose applied. Biological response to radiotherapy dose rates, on the other hand, is a subject of both
5 controversy and ongoing research (Ling *et al* 2010). When taking into account the modulation modern
6 radiotherapy techniques such as VMAT have brought to radiotherapy delivery, two different factors
7 need to be distinguished: On one hand, the treatment machine modulates its output, changing the
8 number of monitor units (MU) per minute (MU rate). On the other hand, every voxel in the
9 calculation volume receives a different dose per time interval, which is referred to as dose rate.
10 Compared to constant dose rates, even less is known about the effects of modulated dose rates. In
11 patient applications, four different orders of magnitude may be examined in radiotherapy dose rate
12 (Murphy *et al* 2007): fractionation schemes in the order of weeks, fraction delivery time lasting
13 minutes, intrafraction modulation from second to second and lastly linear accelerator beam generation
14 in microsecond pulses. Of these four, fractionation schedules have been examined empirically to the
15 greatest extent. Data on intrafraction dose rate, however, hasn't been as comprehensive yet (Ling *et al*
16 2010).

17 In the past, in vitro studies have focused on the effect of protracted dose delivery (lowered
18 dose rate) or treatment interruptions. According to experimental data (Mu *et al* 2003, Wang *et al*
19 2003, Fowler *et al* 2004, Shibamoto *et al* 2004, Ogino *et al* 2005, Joiner *et al* 2010) fractions lasting
20 longer than 20-30 min have to be considered less effective in terms of cell kill than fractions shorter
21 than that. In a first model based approach (Altman *et al* 2006), a simplified IMRT model showed
22 possibilities for increased cell kill when rearranging the IMRT field order especially with increasing
23 fraction delivery time. Bewes *et al.* (Bewes *et al* 2008) confirmed this evidence, but also suggested
24 that "regional variation in the dose rate across a tumor [...] will affect dose efficacy". Although in
25 vitro experiments showed differences in cell kill in the setting of fixed and known dose rates for Co60
26 irradiations (Hall 1972), the actual temporal and spatial distribution of dose rates during a modulated
27 radiotherapy fraction in situ remains unknown.

28 Both IMRT and VMAT use modulation of the MU rate to achieve conformal dose delivery to
29 a tumor and to spare surrounding organs at risk. At any time, only a small part of the target volume is
30 irradiated with the maximum MU rate chosen in the plan. Intrafraction dose rate depends on the same
31 factors affecting dose distribution in tissue, e.g. MU rate, field shape, leakage, tissue composition,
32 distance to source and radiation quality (photons or electrons and their respective energies). It has
33 been proposed by others to analyze these spatiotemporal patterns of dose rate modulation, albeit with
34 a resolution of minutes of radiotherapy delivery (Altman *et al* 2006, Murphy *et al* 2007). As evidence
35 of immediate radiation response initiating DNA damage repair within seconds (Ponette *et al* 2000)
36 and high dose rate treatments (Favaudon *et al* 2014) grows though, the need for a comprehensive
37 analysis of dose rates emerges.

38 This study shows a method to calculate and visualize planned VMAT dose rate distributions in
39 3D and time using MC techniques with sub-second resolution.
40

41 **2. Material and Methods**

42 *2.1. Dose Rate Calculation*

43 In this work, the Swiss Monte Carlo Plan (SMCP) framework (Fix *et al* 2007) was used for all MC
44 dose calculations. Connected to the Eclipse treatment planning system (TPS), the SMCP allows easy
45 integration of a powerful modular MC dose calculation framework offering the choice of several

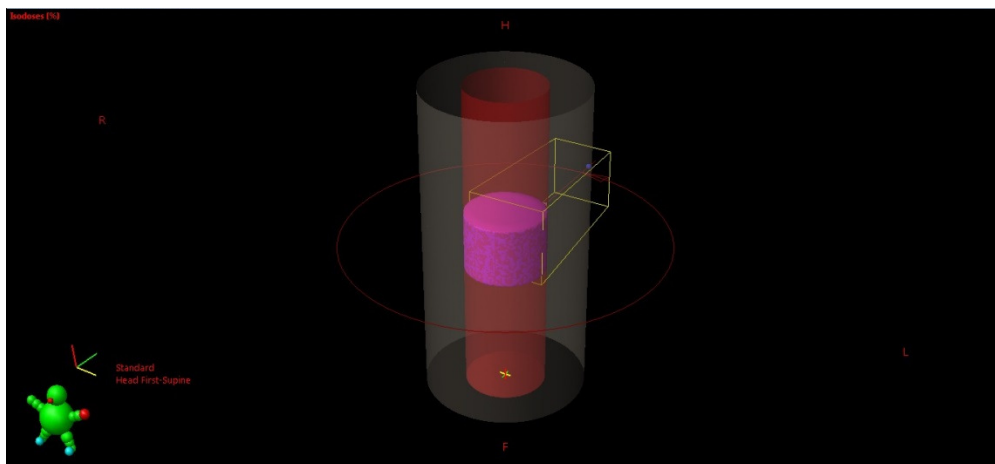
1 currently available particle transport codes. Input to the system may be via the TPS or a proprietary
2 input file format, a combination of which was used in this study.

3 Calculating a dose rate distribution extends the SMCP by the time domain: a dose known to
4 be applied with constant MU rate and the corresponding delivery time are needed. In VMAT
5 treatments, two consecutive DICOM control points (CPs) form one arc sector. As regulated in the
6 DICOM standard, in both IMRT and VMAT treatment, the MU rate is set at each DICOM control
7 point for the following arc sector by the linac. In the system used, the resulting delivery parameters,
8 such as arc sector weight, MU rate in MU per minute, gantry speed and MU per degree are
9 precalculated by the TPS and used by the developed tool. The TPS calculates these parameters taking
10 into account linac specific limitations, e.g. maximum gantry rotation speed, maximum MLC leaf
11 speed or maximum MU rate as set in the plan. Within clinical tolerances, these constraints are
12 assumed to be met by the machine.

13 Starting from an anonymized VMAT DICOM RT plan file, data is read into the TPS for
14 precalculation of MU rates and arc sector times as detailed above. Meanwhile, the same plan file is
15 converted to the proprietary SMCP file format and split into separate files between two consecutive
16 CPs, corresponding to one arc sector each. Any of these files contain all information needed for dose
17 calculation. Typical cases include 100 to 200 CPs per VMAT arc, resulting in a dose delivery time of
18 less than 0.5 s per arc sector. Dose calculations are then performed independently using these files as
19 input, each representing a period of constant MU rate, but dynamic beam angle and field shape. In
20 SMCP, results of the MC calculation are stored in units of cGy per MU (Which can directly be used
21 to calculate the dose rate). By multiplying with the precalculated (constant) MU rate in units of MU
22 per minute, the tool can then store the data as dose rates applied between two CPs for each voxel.

23 2.2. Validation

24 Both the dose rate calculations as well as their visualization were validated with test cases and against
25 measurements.



26 Figure 1: Schematic view of the cylindrical homogeneous water phantom with a diameter of 20 cm
27 used for the validation of dose rate calculations.

28 Artificial test cases were defined in SMCP to validate the dose rate calculations. As a first test
29 case, a virtual cylindrical water phantom with a diameter of 20 cm as shown in figure 1 was generated
30 to create test plans with a fixed source to surface distance to mimic reference conditions as defined for
31 static fields (Almond and Biggs 1999). This phantom was used for dose rate calculations for artificial
32 plans, manually varying the MU rate over the course of an arc in the plan file. Table 1 shows the
33 settings used for three test cases.

1 **Table 1.** Characteristics of artificial treatment plans of a cylindrical homogeneous water phantom
 2 with a diameter of 20 cm used to validate machine compliance to the precalculated MU rates.

Plan	arc sector	1	2	3	4	5	6
1	Gantry angle	0–72°	72–144°	144–216°	216–288°	288–360°	
	MU	600	500	400	300	200	
	MU rate (MU/min)	600	600	600	600	600	
2	Gantry angle	0–72°	72–144°	144–216°	216–288°	288–360°	
	MU	300	100	300	1000	300	
	MU rate (MU/min)	600	400	600	600	600	
3	Gantry angle	0–60°	60–120°	120–180°	180–240°	240–300°	300–360°
	MU	125	125	375	125	125	125
	MU rate (MU/min)	600	600	600	600	600	600

3

4 These test cases as well as the clinical head and neck case were used to validate the machine
 5 compliance to the precalculated MU rates and behavior when switching from one arc sector of fixed
 6 MU rate to the next. Plans were calculated in arc sectors, and resulting dose rate distributions were
 7 checked manually. To preclude calculation errors, arc sector dose rate distributions were multiplied
 8 with their respective application time, summed up and compared against the static Monte Carlo dose
 9 calculation.

10 Measurements were conducted to validate accurate delivery of the synthetic test cases. Plans
 11 were delivered on a Varian Novalis Tx linac to a Delta4 phantom and doses compared arc sector by
 12 arc sector. MU rates were recorded from the linac control panel and compared to the values
 13 precalculated by the TPS and used as input to the SMCP.

14 2.3. Application

15 Three clinical test cases were chosen: A conventionally fractionated head and neck case planned with
 16 4 VMAT arcs, a cranial non-coplanar 4 arc case and a hypofractionated 2 arc liver case.

17 All calculations were performed using MC as transport code to a statistical uncertainty of
 18 about 1% using 0.25 cm edge length calculation grid voxels. Table 2 summarizes the treatment plan
 19 parameters for each of the clinical test cases, with application time describing the time from beam on
 20 to beam off of each arc. Maximum MU rate was set to 600 MU per minute in all cases. All plans were
 21 calculated and dose rate distributions analyzed using the visualization methods described below.
 22 Mean dose rate was calculated as arithmetic mean of all voxels at all time points over one arc within a
 23 volume of interest.

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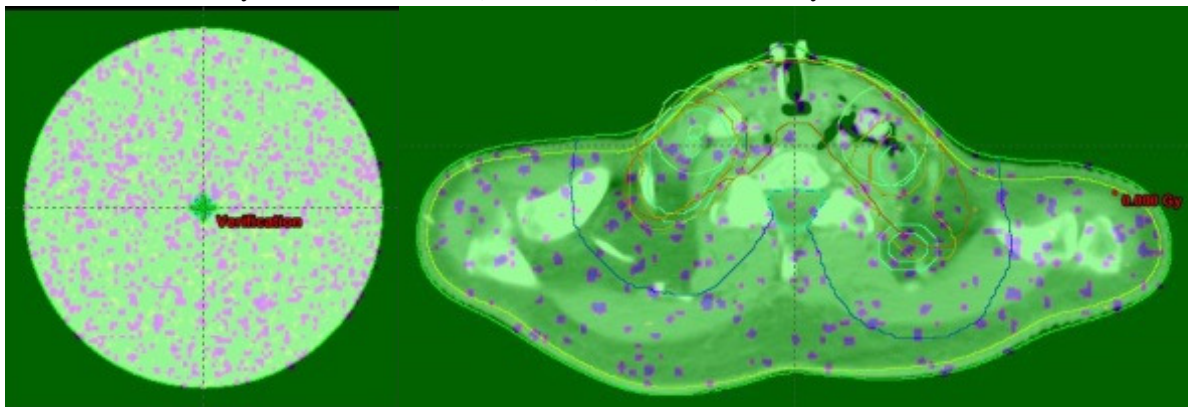
1 **Table 2.** Plan characteristics for three clinical VMAT treatment cases selected for dose rate analysis.

Test case	Prescribed fraction dose (Gy)	Technique	MU per arc	Number of arc sectors	Application time (s)
Head and neck	2	4 VMAT arcs	162	113	41.5
			184	97	36.2
			309	177	74.6
			197	177	74.6
Cranial	2	4 non-coplanar VMAT arcs	123	113	43.5
			117	113	43.5
			58	96	21.9
			58	96	21.9
Liver	5	2 VMAT arcs	732	177	74.6
			552	177	57.1

2 **3. Results**

3 *3.1. Validation*

4 For the artificial test case described in section 2.2. and head and neck case, figure 2 shows the
 5 difference between the dose rates calculated by the dose rate tool multiplied by their corresponding
 6 arc sector times and the static dose distribution calculated by the SMCP. No deviations exceeding the
 7 statistical uncertainty of the calculation (about 1%) were found in any of the test cases.



8
 9 Figure 2: Water phantom and head and neck clinical case with the sum of the dose rate calculation
 10 subtracted from static dose, respectively. Color scale from -0.001 Gy (magenta) to +0.001 Gy (light
 11 green)

12 All plans were applicable without violating any linac specific limitations. Table 3 shows the
 13 recorded cumulative MU and treatment time values. Linac reported standard deviations for MU at
 14 each CP stayed below 0.1 MU in all applications, while the time at each control point deviated less
 15 than 0.4 s from the calculated values. This indicates machine compliance to the planned MU rates. No
 16 treatment prolongation or autonomous alteration of the MU rate by the machine were detected.

17

1 **Table 3:** Treatment delivery records of the three synthetic test cases. For each test case, a fraction was
 2 delivered on a Varian Novalis Tx Linac and the Monitor Chamber and time readings recorded from
 3 the treatment console. Planned values are as precalculated by the TPS.

Test case	ControlPoint	cumulative MU		time (s)	
		planned	recorded	planned	recorded
1	2	600	599	60.0	60.0
	3	1100	1103	110.0	110.4
	4	1500	1499	150.0	150.0
	5	1800	1798	180.0	180.0
	6	2000	2000	200.0	199.8

Test case	ControlPoint	cumulative MU		time (s)	
		planned	recorded	planned	recorded
2	2	300	296	30.0	30.0
	3	400	401	45.0	45.0
	4	700	701	75.0	75.0
	5	1700	1697	175.0	174.6
	6	2000	2000	205.0	204.6

Test case	ControlPoint	cumulative MU		time (s)	
		planned	recorded	planned	recorded
3	2	125	123	12.5	12.6
	3	250	249	25.0	25.2
	4	625	621	62.5	62.4
	5	750	745	75.0	75.0
	6	875	871	87.5	87.6
	7	1000	1000	100.0	100.2

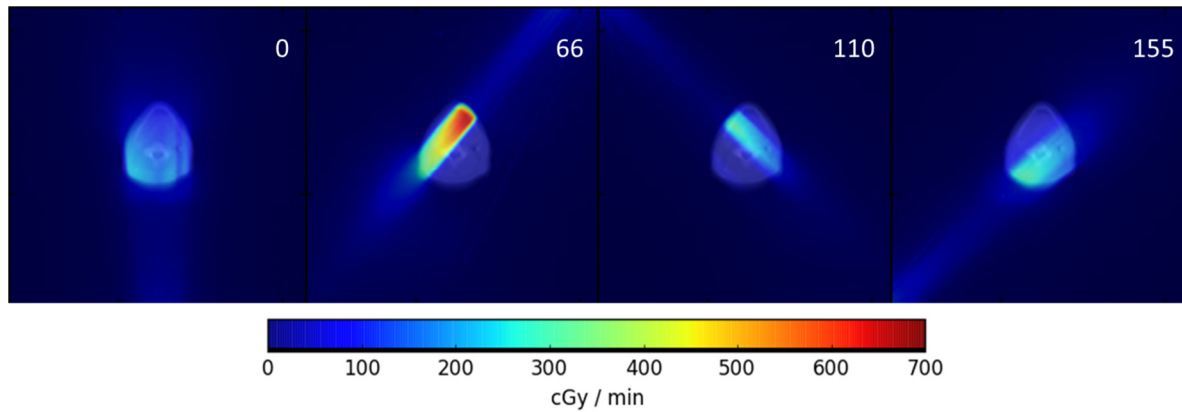
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6 3.2. Visualization

7 Visualization of this 3D plus time data set poses a challenge, as current TPS are not equipped with
 8 time depended dose display routines. Therefore, the calculation tool developed provides a variety of
 9 visualization modes, two of which have proven most useful and will be presented here.

10 To get a view of the dose rates expected in a treatment, the tool provides a statistical analysis
 11 of dose rate over time, neglecting spatial information in the process. Data is presented as a
 12 2D-histogram, showing the number of voxels receiving a certain dose rate in each arc segment. This
 13 mode provides fast analysis of the dose rates expected in a treatment or may be applied to a
 14 subvolume defined in the treatment structure set.

15 On the other hand, in 2D plus time mode, the “color wash” dose display mode is mimicked,
 16 enhanced by a scrollable time dimension. Instead of dose, dose rates are shown to provide all
 17 information about the spatiotemporal variations during the fraction delivery. Example displays for
 18 different arc sectors in one slice of the clinical head and neck case are shown in figure 3. As this mode
 19 provides full spatial information, it is better suited for detailed analysis of the dose rate patterns
 20 emerging in the treatment.



1 Figure 3: Example dose rate distributions of different arc sectors of the first arc of the clinical head
 2 and neck VMAT treatment. Dose rates shown in units of cGy/min in false color, arc sector numbers
 3 shown as white overlay.

4 *3.3. Application*

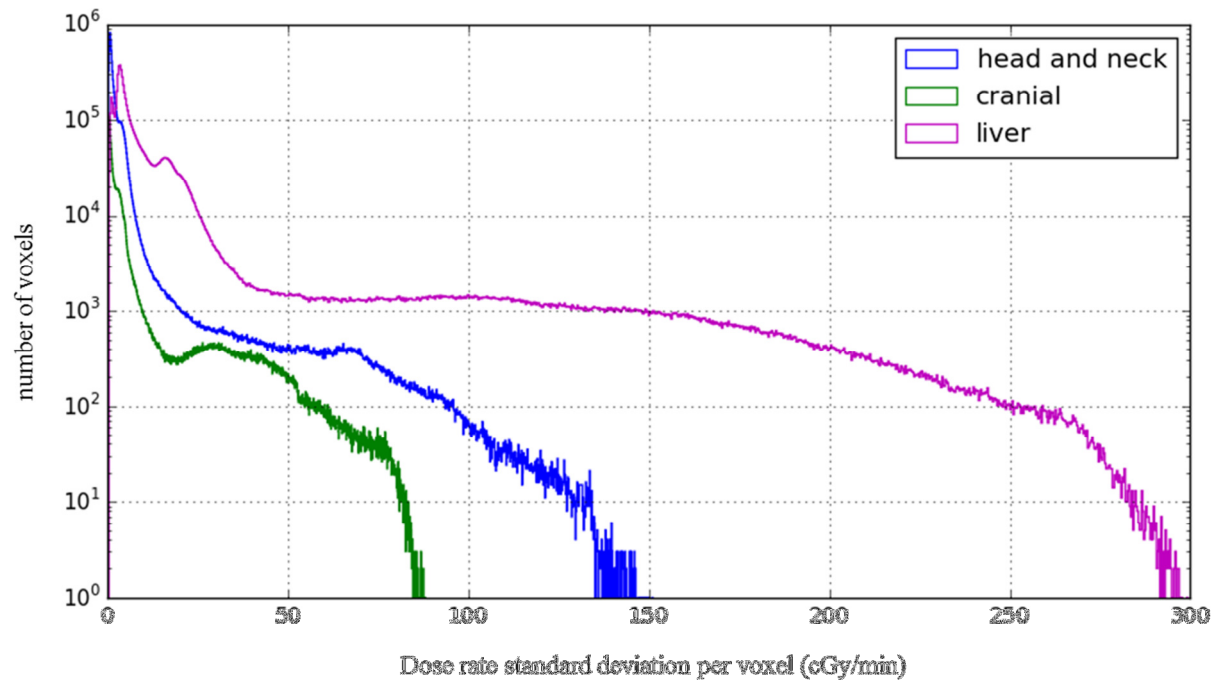
5 For the three test cases selected, table 4 shows the low dose rates encountered in all VMAT
 6 treatments: While maximum dose rates exceed a ratio of 1 cGy/min = 1 MU/min to their
 7 corresponding sector’s MU rate, in each case most of the target volume receives dose rates in the
 8 lower end of the dose rate spectra. In the conventionally fractionated head and neck and cranial
 9 irradiations, mean PTV dose rate hardly exceeds 100 cGy/min. While being an indicator of the
 10 generally low dose rates encountered, mean dose rates are of solely statistical nature as they include
 11 both in- and out of field dose rates. Figure 4 provides a histogram of standard deviations of the dose
 12 rates calculated for individual voxels over the course of one arc. Especially the higher end of the
 13 histogram is of interest here, as this subset of voxels show high variations in dose rates, e.g. if a voxel
 14 received high dose rates alternated by very low dose rates. Maximum standard deviations per voxel
 15 almost double from the cranial case (± 88.1 cGy/min) to the head and neck case (± 151.0 cGy/min) and
 16 again to the hypofractionated liver case (± 299.3 cGy/min).

17 **Table 4:** Minimal, mean and maximum dose rates of voxels within the Planning Target Volume for
 18 three clinical radiotherapy treatment cases.

Test case	Arc	Min. dose rate in PTV (cGy/min)	Mean dose rate in PTV (cGy/min)	Max. Dose rate in PTV (cGy/min)
Head/Neck	1	0.3	70.6	424.8
	2	0.2	75.6	691.4
	3	0.0	39.2	593.6
	4	0.4	47.4	318.1
Cranial	1	2.8	102.3	246.4
	2	2.9	76.6	215.3
	3	2.9	101.6	282.7
	4	1.0	79.9	379.7
Liver	1	5.7	249.3	772.6
	2	6.0	190.9	771.4

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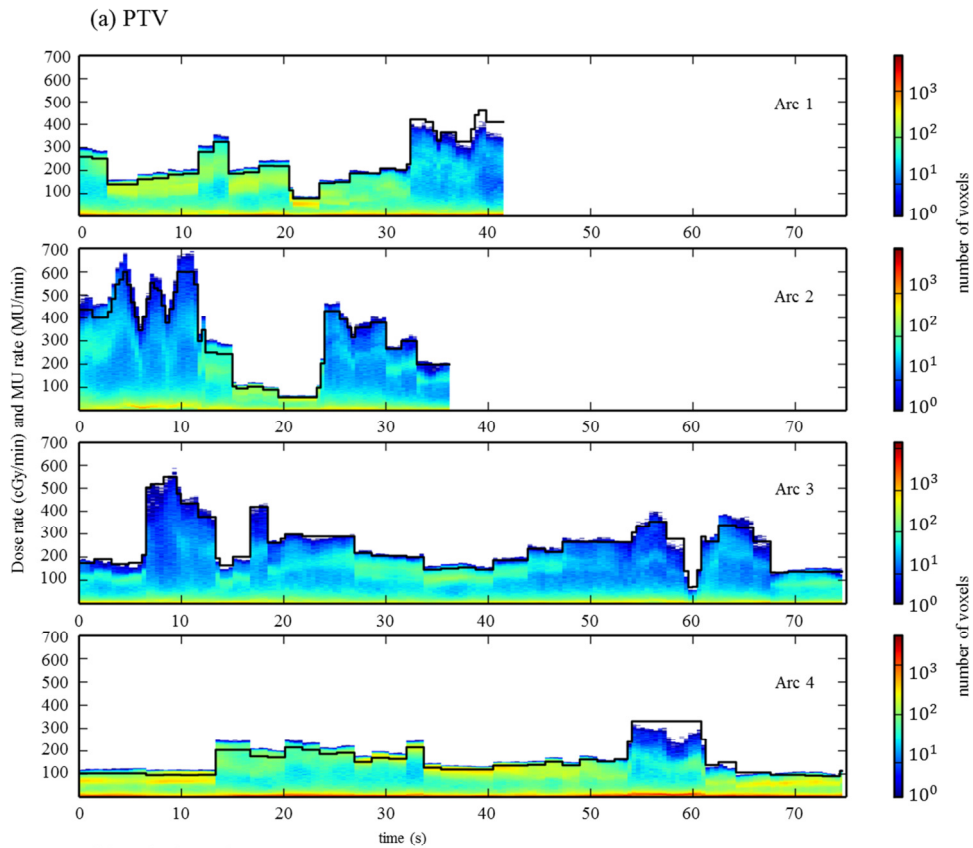


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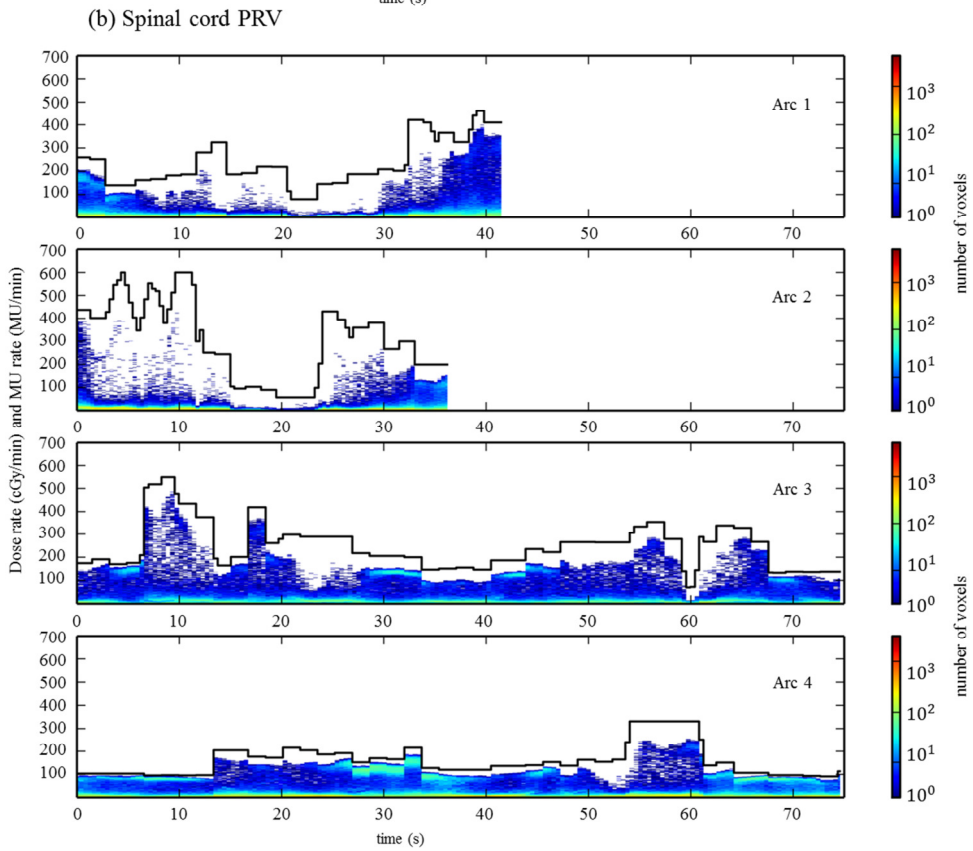
2 Figure 4: Standard deviations of dose rates per voxel of the full calculation volume for the first arc
 3 (see table 2 for reference) of the head and neck (blue), cranial (green) and liver (magenta) cases.
 4 Standard deviations are calculated individually for each voxel from all dose rates seen by this voxel
 5 over the arc considered.

6 Figures 5, 6 and 7 show dose rates (color) and MU rate (black line) in the PTV and an exemplary
 7 organ at risk (OAR) of the head and neck, cranial and liver cases selected. For the head and neck and
 8 liver irradiation, the spinal cord planning risk volume (PRV, spinal cord expanded by a 2 mm margin)
 9 was chosen as OAR, while the cranial case displays dose rates and MU rates in the brainstem.

10

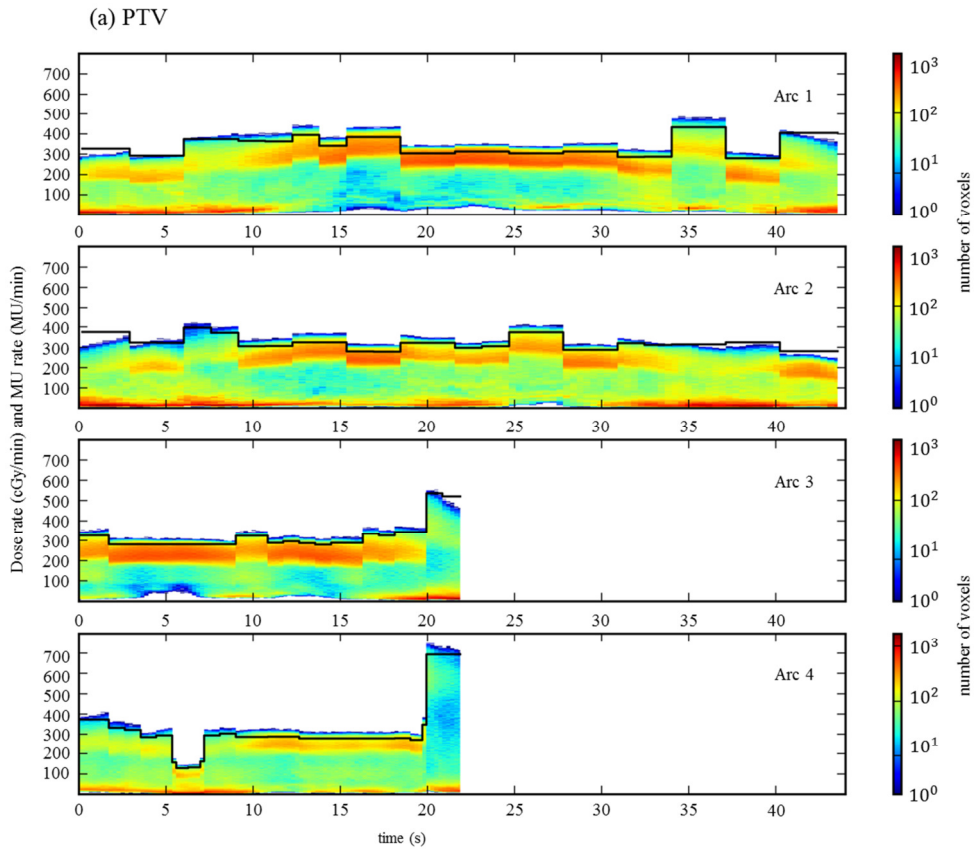


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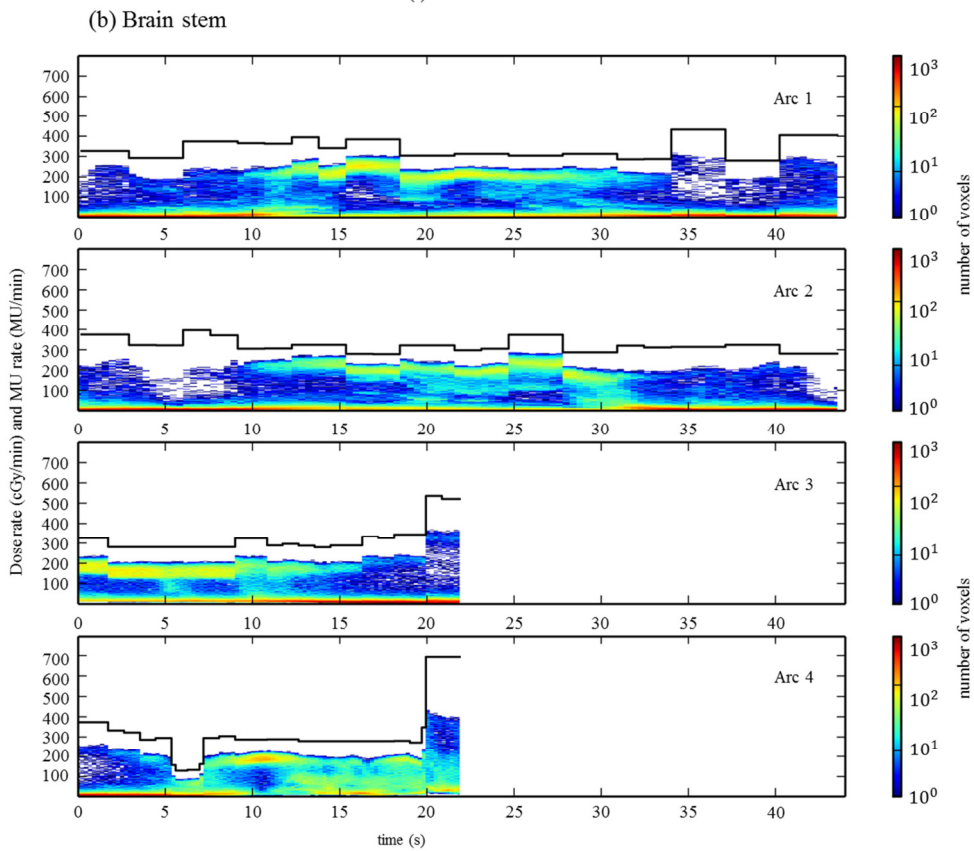


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3 Figure 5: 2D histograms of dose rates (color) and MU rate (black line) in voxels of the PTV (a) and
 4 spinal cord PRV (b), spinal cord expanded by a 2mm margin) in a clinical head and neck case over
 5 all 4 arcs planned. Number of voxels encoded as color on a logarithmic scale.

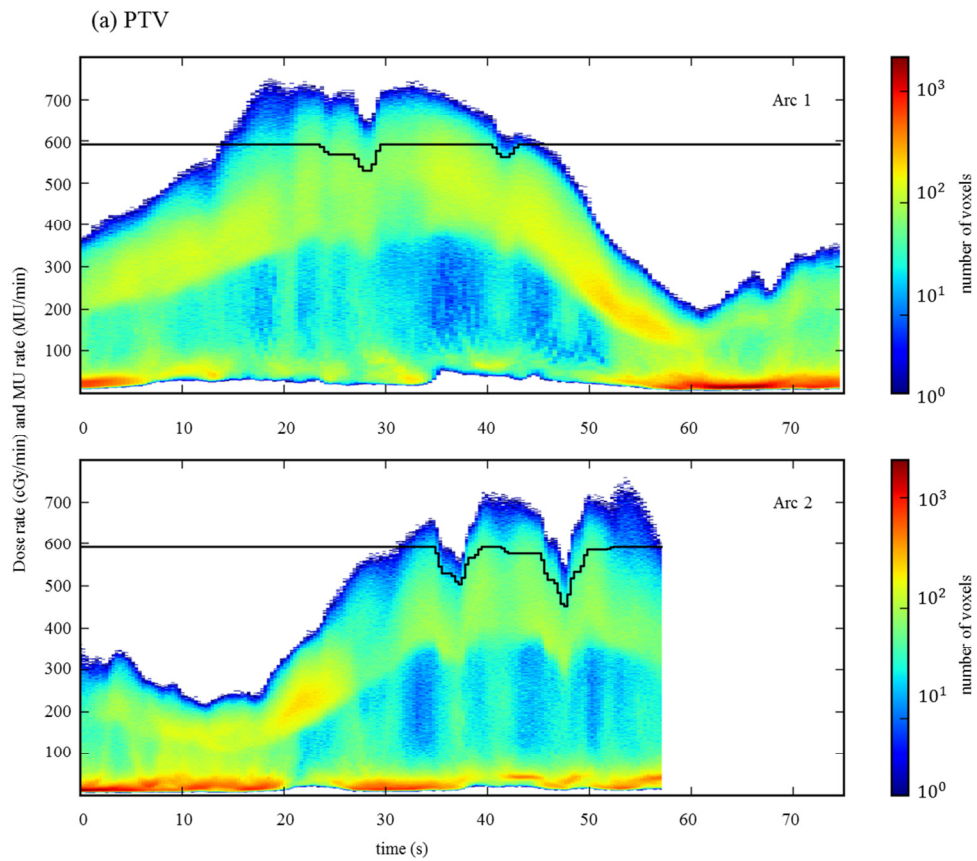


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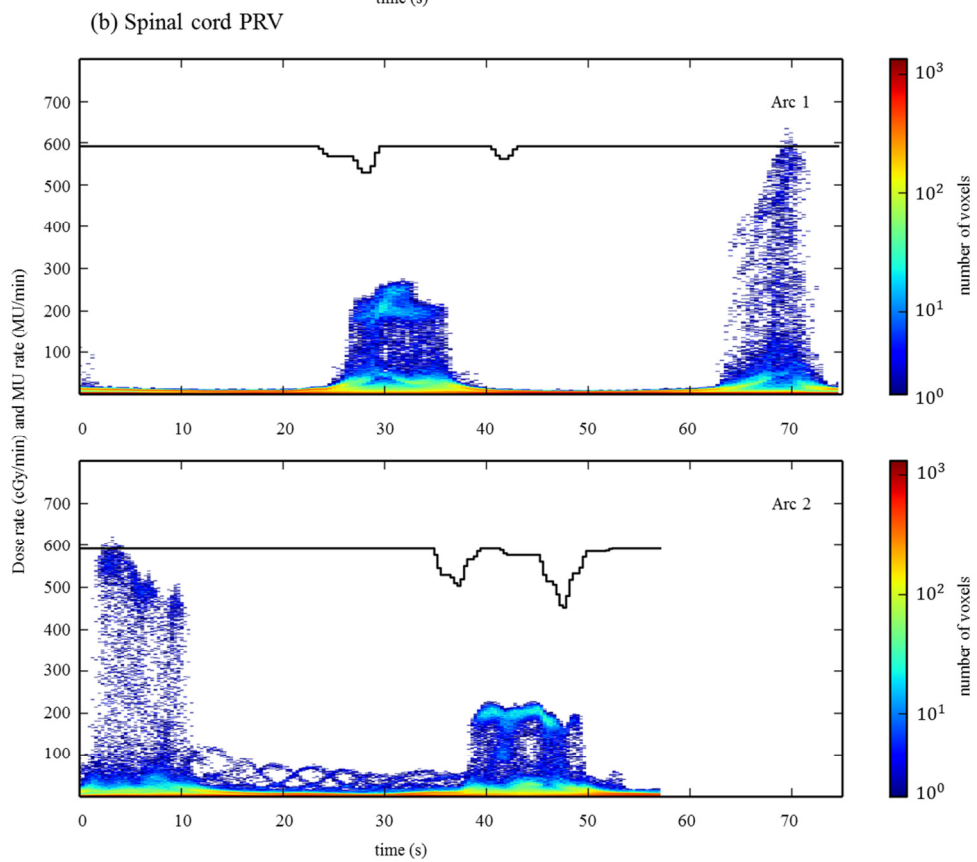


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3 Figure 6: 2D histogram of dose rates (color) and MU rate (black line) in voxels of the PTV (a) and
 4 brain stem (b) in a cranial irradiation case over all 4 arcs planned. Number of voxels encoded as color
 5 on a logarithmic scale.



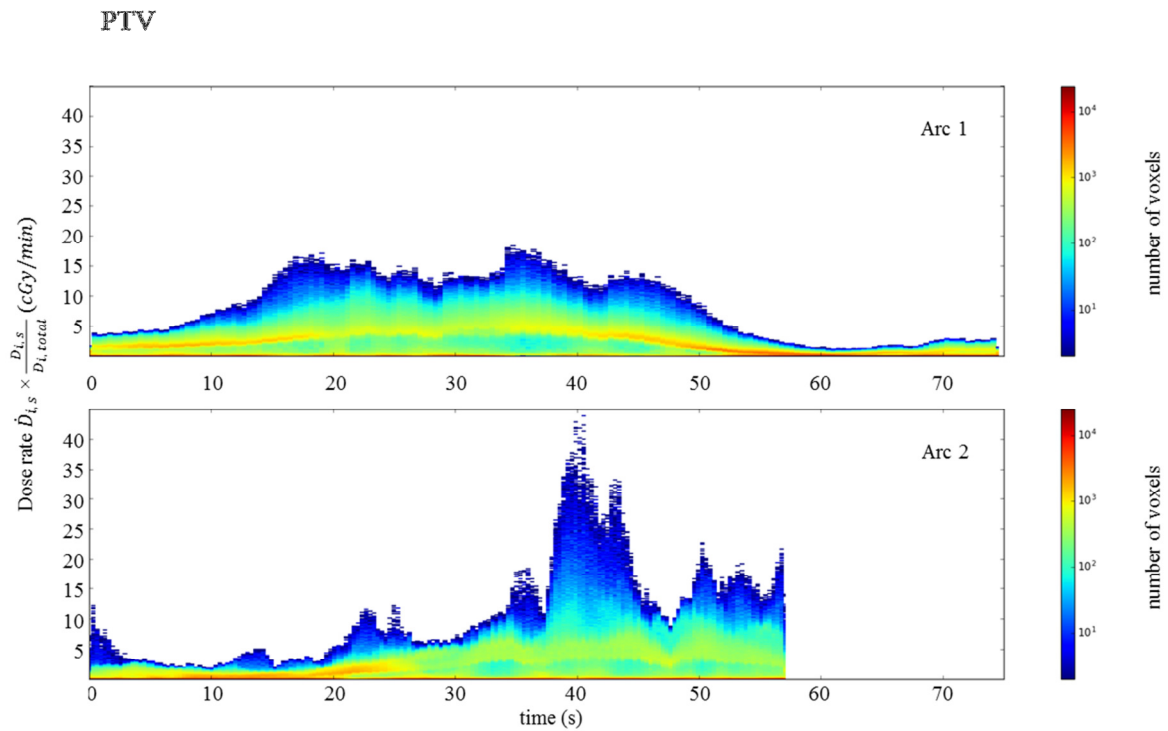
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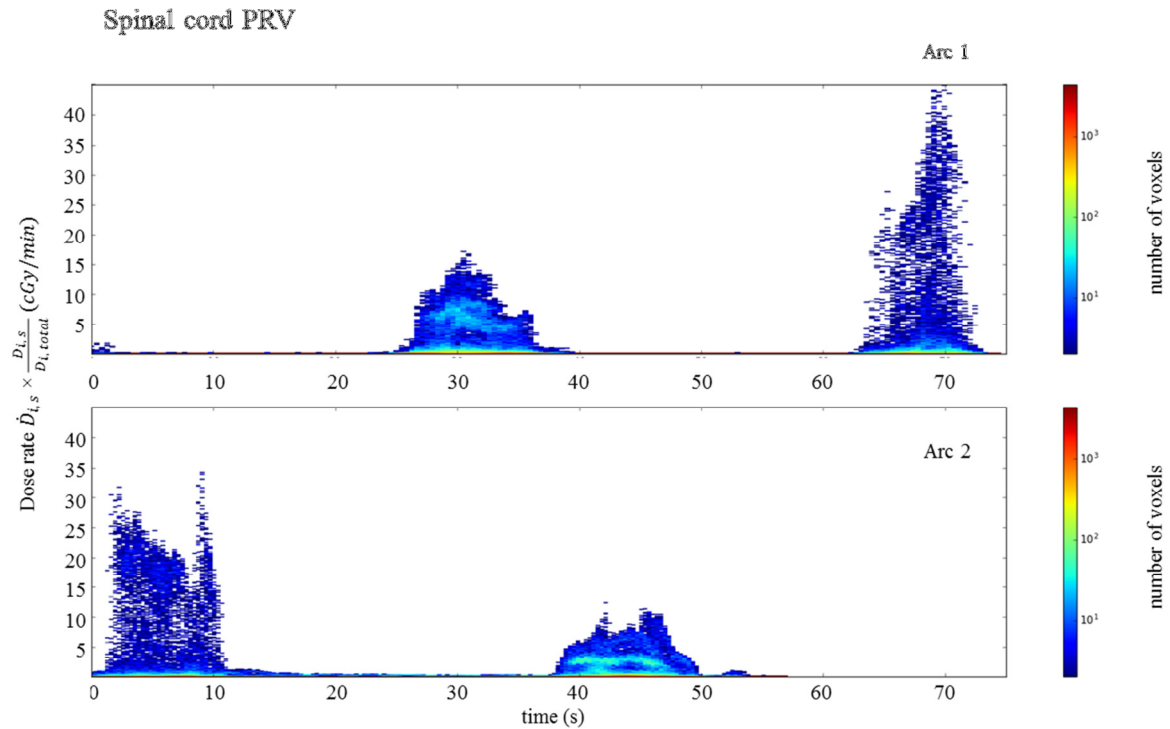
3 Figure 7: 2D histogram of dose rates (color) and MU rate (black line) in voxels of the PTV (a) and
 4 spinal cord PRV (b) in a hypofractionated liver case over all 2 arcs planned. Number of voxels
 5 encoded as color on a logarithmic scale.

1 In order to catch small, but important, dose rate values per voxel contributing most of the dose of this
 2 voxel per arc, figures 8 and 9 show weighted dose rate histograms of the PTV and spinal cord PRV of
 3 the hypofractionated liver case. Each dose rate value was multiplied by the fraction of dose the
 4 corresponding arc sector contributed to the total (per arc) dose of the corresponding voxel. Both
 5 figures show a contribution of a broad spectrum of dose rates to the dose distribution.



6
 7 Figure 8: Weighted dose rate histogram in the PTV of the hypofractionated liver case. Each dose rate
 8 $\dot{D}_{i,s}$ in voxel i and sector s was multiplied by the fraction of dose $\frac{D_{i,s}}{D_{i,total}}$ that sector s contributes to
 9 the total (per arc) dose of voxel i .

10



1

2 Figure 9: Weighted dose rate histogram in the spinal cord PRV of the hypofractionated liver case.

3 Each dose rate $\dot{D}_{i,s}$ in voxel i and sector s was multiplied by the fraction of dose $\frac{D_{i,s}}{D_{i,total}}$ that sector s
 4 contributes to the total (per arc) dose of voxel i .

5 Both the head and neck as well as the cranial test case feature MU rate modulation in blocks of
 6 several arc sectors with dose rates following the pattern. On the contrary, the hypofractionated liver
 7 case modulates both the MU rate and dose rate without any visible grouping. OAR dose rates
 8 generally tend to be lower than those encountered in the PTV, while still showing maximum dose
 9 rates at in-field heights in all of the test cases. In the liver case, the body diameter permits sparing of
 10 the spinal cord for most of the two arcs. Most of the dose to the OAR is delivered by two high dose
 11 rate peaks, showing the case of the spinal cord lying within the beam on the entry and exit side,
 12 respectively. For the head and neck and cranial cases, maximum dose rates to the OAR rarely drop
 13 below 100 cGy/min, despite exhibiting lower MU- and maximum dose rates per voxel. OAR dose
 14 rates are within a smaller range than for the liver case, illustrated by the banding of medium dose rate
 15 voxels in the OAR histograms of the head and neck and cranial cases.

16 4. Discussion

17 A new efficient tool was developed to analyze dose rates per arc sector using MC calculations.
 18 Following the depth dose curve, dose rates vary from values expected at reference conditions, with a
 19 small fraction of voxels even surpassing a one to one ratio between dose rate in cGy/min and MU rate
 20 in MU/min at skin depths smaller than 10 cm. Despite a maximum MU rate set to 600 MU/min,
 21 analysis of the clinical test cases using conventional fractionation showed a substantial fraction of
 22 voxels receiving dose rates below 100 cGy/min. The setting of MU rate in a VMAT radiotherapy plan
 23 merely defines a point of reference in a spectrum of dose rates encountered. Not only may the
 24 machine lower the MU rate according to its limitations in VMAT treatments, rendering dose rates
 25 encountered dependent on the number of arcs and gantry angle travelled (as between the 2-arc and 4-
 26 arc sample cases). But also looking at the clinical test cases revealed that only a small part of the
 27 voxels in the target volume is irradiated with dose rates nearing a ratio of 1 cGy/min = 1 MU/min

1 even below the set maximum MU rate. The more complex the target shape and modulation of the
2 field shape, the larger the fraction of voxels irradiated at low dose rates becomes as shown by the
3 clinical head and neck case selected. These findings may have substantial implications for future
4 research. On one hand, when assessing relative effectiveness of different dose rates in VMAT,
5 radiobiological data correlated to the dose rates encountered needs to be applied. If research should
6 show a reduced effectiveness of lower dose rates or even a threshold for altered effectiveness in low
7 dose rates as it was described by Hall (Hall 1972) for cobalt irradiation, weighting of low dose rates
8 might be adjusted accordingly. Some dose rates may even be low enough for DNA repair to outweigh
9 radiation damage. This would change radiobiological effectiveness during and after phases of low
10 dose rate irradiation, possibly even affecting effectiveness of high dose rates applied afterwards. On
11 the other hand, application of the tool may resolve conflicting evidence. Radiobiological models may
12 be verified and clinical findings explained by the new insights provided.

13 All of the clinical treatment plans considered show arc sector times in the order of 0.2 - 0.4 s,
14 achieving sub-second resolution of the calculated dose rate distributions, but still suffering from
15 averaging. The dose rates shown leverage the DICOM convention to keep dose rate constant between
16 two consecutive control points even in modulated treatments. Recordings of synthetic test cases
17 confirmed that MU rates are not being interpolated, but kept constant between control points. Similar
18 to partial volume effects, voxels changing their dose rate between control points due to movement are
19 assigned an averaged dose rate, leading to “partial time effects” in areas of high dose rate gradients.
20 Further, dose rates reported are calculated values only, focusing on planning stage. Similar to the
21 calculation of dose distributions, any deviations between planned and delivered dose rates, caused for
22 example by the linac MU feedback loop, are not considered in this work. The tool developed focuses
23 on VMAT as dose rate variations are more emphasized in this technique compared to IMRT, but its
24 algorithm is applicable to both step and shoot and sliding-window IMRT as well. There definitely is a
25 need to further improve resolution of dose rate analysis. So far, dose rate can be plotted with respect
26 to time, but not tissue. Dose rate effect is believed to vary with tissue (Favaudon *et al* 2014, Steel *et al*
27 1986) and should thus be weighted accordingly between e.g. tumor tissue and organs at risk. So far,
28 the tool can only give dose rate distributions for each organ separately, but not visualize them
29 together. These may be used to provide a “deconvolution” of the spatio-temporal patterns of dose
30 rates in VMAT to apply fixed dose rate evidence to these de-facto modern standard treatment
31 techniques. It would be interesting to see radiobiological and clinical research interpret these values.
32 In clinical routine, these data could aid deciding between treatment modalities of different dose rates,
33 such as flattened versus flattening filter free beams or conventional versus hypofractionation. With the
34 advent of new fractionation schemes, knowledge about dose rates would allow to choose a
35 fractionation scheme tailored to the dose rates encountered in specific regions of interest. Radiation
36 effect to the tumor could be tailored according to dose rate models as could damage to each organ at
37 risk individually. As modelling of dose rate response evolves (Herr *et al* 2014), this tool serves as an
38 insight into dose rates encountered in modulated radiotherapy treatments and hopes to aid and guide
39 further investigation.

40 **5. Conclusion**

41 A tool to analyze planned dose rate distributions with sub-second accuracy was successfully
42 developed and validated. Visualization is done via histogram distributions of dose rates in regions of
43 interest over a treatment fraction or 2D plus time display as color wash. Dose rates per arc segment
44 encountered in clinical VMAT cases show a continuous spectrum of dose rates with a mean value in
45 the lower part of the spectrum for both conventional fractionation and for a hypofractionated liver
46 case. Dose rate distributions in modulated radiotherapy can now be assessed, and will serve as input
47 for further radiobiological study. In the future, these data could aid deciding between treatment

- 1 modalities of different dose rates, such as conventional versus hypofractionation. Fractionation
2 schemes might even be tailored to the dose rates encountered in specific regions of interest.
- 3
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