Definition of dose rate in conformal FLASH particle therapy: a comparative study

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Background: FLASH proton therapy has the potential to reduce side effects of conventional proton therapy by delivering a high dose of radiation in a very short period of time. However, significant progress is needed in the development of FLASH proton therapy. Increasing the dose rate while maintaining dose conformality may involve the use of advanced beam-shaping technologies and specialized equipment such as 3D patient-specific range modulators, to take advantage of the higher transmission efficiency at the highest energy available. The dose rate is an important factor in FLASH proton therapy, but its definition can vary because of the complex way in which the beam is scanned and the uneven distribution of the dose over time in pencil beam scanning (PBS).
Purpose: To highlight the distinctions, both in terms of concept and numerical values, of the various definitions that can be established for the dose rate in PBS proton therapy.
Methods: In an *in silico* study, five definitions of the dose rate, namely the PBS dose raten the relative-threshold dose rate (RT dose rate), the percentile dose rate, the dose averaged dose rate (DADR) and the average dose rate, were analyzed first through theoretical comparison, and then applied to a head and neck case. To carry out this study, a treatment plan utilizing a single energy level and requiring the use of a patient-specific range modulator was employed. The dose rate values were compared both locally and by means of dose rate volume histograms (DRVHs).
Results: The PBS dose rate, the RT dose rate, and the percentile dose are definitions that are specifically designed to take into account the time structure of the delivery of a PBS treatment plan. Although they may appear similar, our study shows that they can vary locally by up to 10%. On the other hand, the DADR is approximately twice as high as the 'percentile type dose rates' since it disregards the periods when a voxel does not receive any dose. The averaged dose rate can be defined in various ways, as discussed in this paper. Using a conservative approach, in which the dose rate is calculated individually for each voxel, taking into account the periods when the voxel does not receive any dose, the averaged dose rate is found to be lower by a factor of approximately 1/2 than the 'percentile type dose rates'.
Conclusions: We have demonstrated that different definitions of the dose rate in FLASH proton therapy can result in variations in calculated values from a few percent to a factor of 2. As the dose rate is a crucial parameter in FLASH radiation therapy, it is important to carefully consider the choice of definition. We have discussed the conceptual differences regarding the uncertainty that exists about the time scale related to the FLASH effect and given which it is currently not possible to determine which definition is the most suitable. We have raised several key questions that need further biological data and models to be answered.

Keywords: FLASH, Flash Proton Therapy, Dose Rate

I. INTRODUCTION

FLASH radiation therapy has gained increasing interest in recent years due to its potential to significantly reduce side effects associated with radiation therapy at conventional dose rates[1–3]. By definition, a FLASH treatment corresponds to delivering a high dose of radiation in a very short period. While more research is needed to fully understand the potential benefits and limitations of FLASH proton therapy as well as the underlying mechanism[4–7], there is a growing number of research studies on treatment delivery and treatment planning.

One of the main challenges in developing FLASH proton therapy is the need to significantly increase the dose rate or the amount of radiation delivered per unit of time. To achieve a FLASH dose rate, a number of changes are needed to the equipment and delivery system used in intensity modulated proton therapy (IMPT). In particular, the proton beam must be delivered at a much higher energy than is generally used in IMPT to ensure a high transmission efficiency[8]. This may involve the use of advanced beam-shaping technologies as well as specialized nozzle designs and dosimetry equipment.

To obtain a conformal treatment plan with a single high energy layer, the range of the proton beam must be adjusted by using a range modulator, which is a device

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that is placed between the nozzle and the patient[8]. The range modulator passively adjusts the energy of the proton beam, which in turn affects the depth at which the protons will deposit their energy in the patient's body. Several planning methods have been proposed to optimize such range modulators[9–12].

Besides the calculation of the range modulator, another challenge in planning is to calculate the spot map in order to maximize the dose rate. In addition, the scanning pattern of the pencil beam scanning (PBS) spots may also be optimized[13].

Both for preclinical experiments and for the development of planning and delivery tools, the dose rate is the key parameter in FLASH. Unfortunately, in proton therapy, defining the dose rate is not trivial. Indeed, The beam is scanned such that a voxel receives its total dose through a series of contributions unevenly distributed over time. It is therefore not surprising that in the literature the definition used for the dose rate varies from one publication to another[14].

To define the dose rate, three factors must be taken into consideration:

- The structure of the pulses;
- The dose delivered by each PBS spot;
- The time-related contribution to the dose seen by each voxel.

Calculated over the duration of a pulse, the dose rate can vary by several orders of magnitude, depending on the beam delivery mode as a cyclotron produces a near-continuous beam delivery while a synchrocyclotron produces a pulsed beam with an instantaneous dose rate significantly higher but with a duty cycle significantly lower[8]. It is often assumed that the time scale related to the FLASH effect is larger so that the dose rate may be considered constant during the delivery of a spot[15–17], although this remains to be demonstrated[14]. Nevertheless, in PBS, the total dose received by a voxel is generally the sum of the contributions of several spots. Therefore, the dose rate may be computed independently for each voxel, taking into account both the dose contributions and the temporal structure of these contributions, as proposed by Folkerts *et al.*[15] which established the so-called definition of the 'PBS dose rate' which is very similar to the concept of 'percentile dose rate' proposed by others[16,17] and which is referred to as 'relative-threshold dose rate' in this paper, as not to be confused with the general 'percentile dose rate' which will also be introduced.

In the next sections, we first introduce different definitions of dose rate based on a review of the literature. We also generalize the concept of percentile dose rate. These definitions are then compared and discussed. A conformal FLASH treatment on a head and neck case was used to carry out this *in silico* assessment. Through this experiment, we show how the definition can impact the calculated dose rate values by several percent.

II. MATERIALS AND METHODS

A. Dose rate definitions

In PBS, the dose is delivered by spots separately temporally by 'beam-off' times. Depending on the voxel in which we compute the dose rate, the temporal structure of contribution to the dose may vary. Therefore, we establish the following definitions which will be used to define the dose rates.

- $d_i(t)$ is the instantaneous dose received in voxel i at time t;
- $t_i(d)$ is the time elapsed to obtain dose d at voxel i;
- $D_{i,s}$ is the total dose contribution of spot s to voxel i;
- D_i it the total accumulated dose received in voxel i: $D_i = \sum_s D_{i,s}$;
- T_s is the total irradiation time ('beam-on' time) of spot s.

1. PBS (Varian) dose rate

The PBS dose rate was defined by Folkerts *et al.*[15] to account for the time structure of the delivery of a PBS treatment plan:

$$\dot{D}_i^{PBS} = \frac{D_i - 2D^{Th}}{t_{1,i} - t_{0,i}} \tag{1}$$

where $t_{1,i} = t_i(D_i - D^{Th})$, $t_{0,i} = t_i(D^{Th})$, and D^{Th} is an arbitrary dose threshold.

This dose threshold is often computed as a percentage of the prescription: $D^{Th} = p \times$ prescription with p being an arbitrary percentage. For example, to compute the dose rate on an interval corresponding to 95% of the dose, we would use $p = 2.5\%$.

Fig. 1 illustrates this definition for $p = 0.025$ through an hypothetical example where the total dose received by the voxel is 10 Gy which is also assumed to be the prescription. It can be seen that the time window extends from the moment when the dose reaches 0.25 Gy until the moment when it reaches 9.75 Gy.

2. Relative threshold dose rate

In the definition of the PBS dose rate, the dose threshold is a fixed value, which can be a percentage of the prescription. This arbitrary choice is questionable outside the target volume where the dose is expected to be much lower than the prescription. In particular, for low doses, the PBS dose rate might be undefined. For example, for a prescription of 70 Gy and $p = 0.025$ the PBS

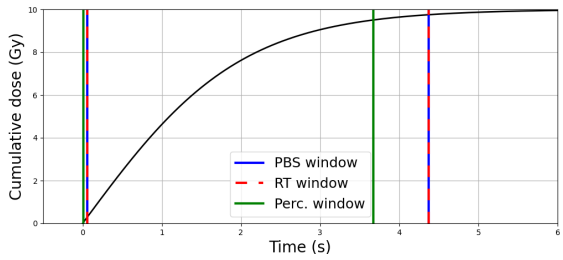

FIG. 1. Time windows according to each of the three 'percentile type definitions' for $p = 0.025$ and an arbitrary cumulative dose profile corresponding to a prescription of 10 Gy.

dose threshold is 1.75 Gy. Therefore, the PBS dose rate cannot be computed in any voxel presenting a dose lower than two times this value, i.e. 3.5 Gy.

The definition of the PBS dose rate can easily be adapted so that the threshold is proportional to the dose delivered to the voxel:

$$\dot{D}_i^{RT} = \frac{(1-2p)D_i}{t_{1,i} - t_{0,i}} \tag{2}$$

where $t_{1,i} = t_i((1-p)D_i)$, $t_{0,i} = t_i(pD_i)$, and p is an arbitrary percentage.

This definition was used by IBA (Ion Beam Applications SA, Louvain-la-Neuve, Belgium) in several conference communications[16,17] and implemented in their conformalFLASH library (openflash.sofwtare).

3. Percentile dose rate

According to both definitions above, the PBS and RT dose rates are computed over a window of time. The position of the window is defined as the moment, named t_0, when the dose exceeds an arbitrary threshold. The definition of time t_0 could actually have a significant impact on the calculated value. For example, if we choose $p = 2.5\%$, there certainly exist several windows of different widths and starting points covering 95% of the dose.

The percentile dose rate generalizes the concept of RT dose rate by considering all time windows in which the accumulated dose is at least $(1-2p)D_i$:

$$\begin{aligned} \dot{D}_i^{PERC} &= \max_{t_0,t_1} \frac{\int_{t_0}^{t_1} d_i(t)dt}{t_1 - t_0} \\ & s.t. \int_{t_0}^{t_1} d_i(t)dt \geq (1-2p)D_i \\ & t_1 > t_0 \end{aligned} \tag{3}$$

In this formula, the calculated time window is the one that gives the maximum dose rate while respecting the constraint that the cumulative dose is greater than an arbitrary percentage of the total dose delivered to the voxel.

We can see from the hypothetical example of Fig. 1 that this definition provides a different time window than those of the PBS and the RT dose rates. Indeed, the 95-percentile dose rate window begins at $t = 0$, when the cumulative dose is still zero, and ends when the cumulative dose in the voxel reaches 9.5 Gy. Although the cumulative dose is 9.5 Gy for the 3 definitions, the time interval is shorter in the case of the 95-percentile dose rate, which gives a higher dose rate value. This example remains purely theoretical and is presented in order to clearly visualize the differences that may exist between these three definitions. We will later apply them to a clinical case in order to discuss the implications.

In our implementation, the percentile dose rate was efficiently computed by means of sliding windows where t_1 was defined as $t_1 = t_0$+window width. The sliding of this window over d_i was implemented as a cross-correlation product, for each window width. As the cross-correlation product is related to the convolution product, it can be efficiently computed via a fast Fourier transform.

At first glance, this implementation might seem similar to the sliding window defined by Schwarz *et al.*[18] which proposed a metric related to the 'Flash effectiveness model' proposed by Krieger *et al.*[19]. However, in the method of Schwarz *et al.*, the dose threshold and the dose rate are used as input to define the time window to be slid over the accumulated dose contributions. For example, a threshold of 4 Gy for a dose rate of 40 Gy/s gives a window width of 100 ms. This window would then be slid to determine when the dose is greater than 4 Gy. On the other hand, a threshold of 40 Gy would give a window of 1 s. With this much larger window, dose contributions considered invalid with the 4 Gy threshold could now end up valid since only the dose accumulated over the time window matters. This might seem inconsistent but the main issue with the definition of the sliding window in Schwarz *et al.* might be that to compute the window width, we must first specify the dose rate. Paradoxically, the dose rate is precisely the quantity that we seek to determine. For this reason, we have not considered this definition in the present study.

4. Dose-averaged dose rate

The dose-averaged dose rate (DADR) is one of the first dose rate definitions established specifically for FLASH proton therapy by van de Water *et. al.*, in 2019[20].

In the DADR, the instantaneous dose rate is first, averaged over the spot duration, ie. $\frac{D_{i,s}}{T_s}$ is computed for each spot s. Then, these contributions to the dose rate are weighted by the dose contribution of each spot to the voxel:

$$\dot{D}_i^{DA} = \frac{\sum_s D_{i,s} \frac{D_{i,s}}{T_s}}{D_i} \tag{4}$$

Consequently, the DADR neglects not only the 'beam-off' times but also the time during which the voxel does

not receive any dose because the system is irradiating a distant position.

5. Average dose rate

The average dose rate is sometimes used in the literature without a clear definition being specified by the authors. However, as we have seen previously, some authors consider that 'beam-off' times, or even the time when a voxel does not receive any dose, should not be taken into account, while others include them in their definitions. Other considerations could also enter into the definition:

1. Averaged dose rate defined per spot:
   (a) Average of the pulse instantaneous dose rates without taking into account the beam-off times.
   (b) sum of instantaneous doses for this spot divided by the time required to irradiate the spot (including beam-off times between pulses).
2. Averaged dose rate defined per field:
   (a) Average of the spot dose rates without taking into account the scanning times.
   (b) Total dose divided by the total duration of the field irradiation, including scanning times.
3. Averaged dose rate defined per voxel:
   (a) Dose-averaged dose rate.
   (b) Total dose delivered to the voxel (at the end of the plan irradiation) divided by the duration to deliver the field: $\dot{D}_i^A = \frac{D_i}{T_{total}}$.
   (c) 100th-percentile dose rate: $\dot{D}_i^A = \frac{D_i}{t_{1,i} - t_{0,i}}$ where $t_{0,i}, t_{1,i}$ are respectively the time at which voxel i starts to receive some dose and the time at which the total dose for that voxel is reached.

A conservative approach is of course to calculate the dose rate individually for each voxel also considering the time periods when it does not receive any dose as in Def. 3b and 3c. However, it is clear that following such logic, Def. 3c is to be preferred. Indeed, let us imagine, as an example, that we have to add to the treatment plan a spot far from voxel i, so far that it is impossible for it to contribute to the total dose delivered to voxel i. With Def. 3b, the irradiation time of this spot would be taken into account which would decrease the estimated dose rate. This is not the case with definition 3c which understands that voxel i has already received its full dose when this additional spot is delivered. Hence, for the average dose rate, the definition used in the remainder of this paper is Def 3c.

B. In silico assessment

The different dose rate definitions were applied to a FLASH conformal treatment plan calculated with the method presented by Deffet *et al.*[12]. In this paper, a treatment plan was optimized on a head and neck case which is reused in the present publication. We considered the PTV with a prescription of 70 Gy presented in Fig. 3. According to the publication of Deffet *et al.* the treatment plan and its associated range modulator were computed for an energy of 226 MeV, a spot size of ($\sigma_x = 4.5$ mm, $\sigma_y = 5$ mm), and a spot spacing of 3 mm.

To facilitate the comparison of the different dose rate formulas, we used a simple model where:

1. the nozzle output current was considered constant;
2. the time between 2 spots was proportional to the distance between the spots.

In other words,

1. the irradiation time of a spot was the ratio between the charge of the spot and the current;
2. the time separating 2 spots was the ratio between the distance of the spots and an assumed scanning speed.

The spots were ordered in a serpentine pattern, according to the IBA clinical system. The current was 350 nA (averaged on a pulse period) at the output of the nozzle and the scanning speed was 8000 mm/s. With those inputs, a timeline showing the start and end of each spot can be drawn, such as in Fig. 2.

A dose influence matrix was calculated using MCsquare[21] to determine the contributions of each spot to the dose of voxel i. The joint use of the timeline and the dose influence matrix was used to compute for each voxel i the dose integrated over time, or its reciprocal, ie. the time to go from one dose threshold to another.

III. RESULTS

A. Percentile, PBS, and RT dose rates

As emphasized in the previous section, the delivery pattern and time structure of the PBS spots are of utter importance when defining the dose rate, in proton therapy. Factors such as the sequence in which the spots are delivered, the spacing between the spots, the overall shape of the pattern, and the scanning frequency should be considered. Fig. 2 shows the scanning pattern and the corresponding temporal structure of the dose contributions. The irradiation time of each spot is proportional to the charge, as a result of our simplified model which relies on the assumption of a constant current. This figure also shows that the time between two distant spots does not depend so much on the distance as such but

rather on the cumulative charge that must be delivered between these two spots.

Because the first three definitions are based on some percentage of the delivered dose, we refer to them as 'percentile type dose rates'. The corresponding maps of dose rates are shown in Fig. 3, for $p = 0.025$. As explained previously, this value corresponds to a 95-percentile dose rate. We also evaluated the dose rate for other values ranging from the $p = 0.05$ (90-percentile) to $p = 0.005$ (99-percentile) and we always observed very similar trends, hence we only show results for $p = 0.025$.

Globally, the percentile dose rate is higher. The RT dose rate and the PBS dose rate look more similar although differences are noticeable. We selected two locations on this map to better understand those differences.

At point A, the RT dose rate is equal to the PBS dose rate but the percentile dose rate is higher. In Fig. 4, the plot of the time windows corresponding to each of the dose rates gives a visual explanation. While, by definition, the percentile dose rate selects the shortest window out of all possible windows, for the other two definitions the size of the time window depends on the instants at which the dose exceeds a lower threshold and an upper threshold. In that voxel, the RT dose rate is equal to the PBS dose rate as the delivered dose perfectly corresponds to the prescription.

At point B however, the PBS dose rate is higher and the percentile dose rate is equal to the RT dose rate. At this location, the dose is well below the prescription as it is outside the PTV. Namely, the dose is exactly 16.6 Gy. However, the PBS dose rate defines the thresholds to be taken into account for the calculation of the time window based on a percentage of the prescription which is 70 Gy. On the contrary, the RT dose rate defines the thresholds based on a percentage of the total dose delivered in the voxel. It is therefore obvious that the width of the window of the RT dose rate is larger than that of the PBS dose rate, leading to a different dose rate value. On the other hand, no difference is observed between the percentile dose rate and the RT dose rate which comes from the cumulative dose profile which is almost symmetrical around its inflection point.

As the dose rate varies locally, it seemed natural to present the quantity of volume irradiated under a certain dose rate in the form of a dose rate volume histogram (DRVH), similar to what is done for the dose[15]. For the evaluation of a FLASH treatment, it seems logical to assess the dose rate in the organs at risk and the healthy tissues surrounding the target volume. However, in order to facilitate the comparison, we did not define a volume for each OAR but rather a unique volume surrounding the PTV. To draw this volume, we first computed an extension of 15 mm of the PTV (PTV subtracted from the dilated PTV), named PTV-ext, from which we excluded areas where the dose was lower than 1 Gy. Hence, the DRVHs were calculated on two volumes: on the PTV which is supposed to receive a uniform dose of 70 Gy, and on PTV-ext which should receive a lower dose.

	DR2	DR5	DR50	DR95	DR98
PTV, $(1-2p) = 95\%$					
PBS dose rate	73.88	63.62	38.58	31.24	29.38
RT dose rate	83.40	71.03	41.37	32.47	30.24
Percentile dose rate	98.51	82.76	43.14	33.68	31.44
PTV-ext, $(1-2p) = 95\%$					
PBS dose rate	73.93	65.94	29.51	5.41	3.85
RT dose rate	81.95	71.95	28.94	3.49	2.16
Percentile dose rate	96.87	84.48	31.05	3.76	2.37

TABLE I. DRx metrics (Gy) associated with the DRVHs of the dose rates of percentile type.

	DR2	DR5	DR50	DR95	DR98
PTV					
DADR	220.71	215.28	169.86	123.90	112.86
Av. dose rate	48.28	43.66	30.72	24.26	22.63
PTV-ext					
DADR	222.47	215.83	117.36	17.28	12.91
Av. dose rate	47.31	42.87	20.30	2.66	1.54

TABLE II. DRx metrics (Gy) associated with the DRVHs of the dose rates of averaged type.

The DRVHs shown in Fig. 5 and the associated metrics listed in Table I confirm the results presented above. Firstly, the PBS and the RT dose rates are very similar in the PTV since the dose is very close to the prescription. Second, the percentile dose rate is higher than the PBS and the RT dose rates, except in PTV-ext where the coverage of the RT dose rate is better for low dose rates.

B. Average dose rate and DADR

The two 'averaged type' dose rates considered in this paper exhibit two opposite trends. On the one hand, as shown on Fig. 5 and in Table II, the DADR is approximately twice as high as the 'percentile type dose rates' since it discard, for each voxel, the periods when it does not receive any dose. On the other hand, the averaged dose rate is the lowest dose rate encountered so far as it is equivalent to a 100-percentile dose rate.

IV. DISCUSSION

In proton therapy, numerous considerations should be taken into account when defining the dose rate in FLASH. One of the most important is the need to take into account the delivery pattern of the PBS spots and to a lesser extent the 'beam-off' times. A voxel in the patient may receive dose contributions at different times. These contributions can be separated by several milliseconds and we showed that the way this is accounted for

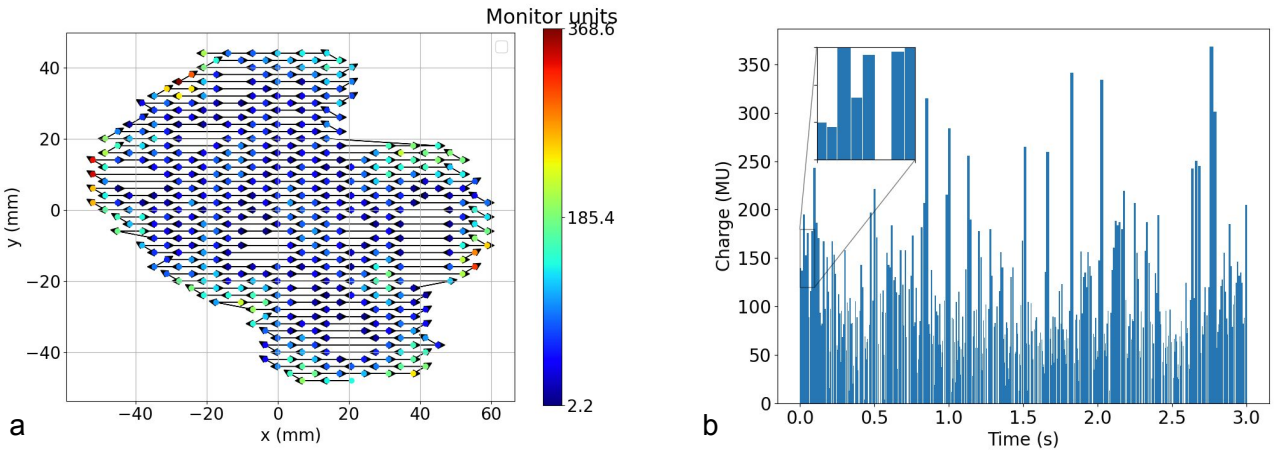

FIG. 2. (a) Delivery pattern of the PBS spots, and (b) time-structure of the dose delivery.

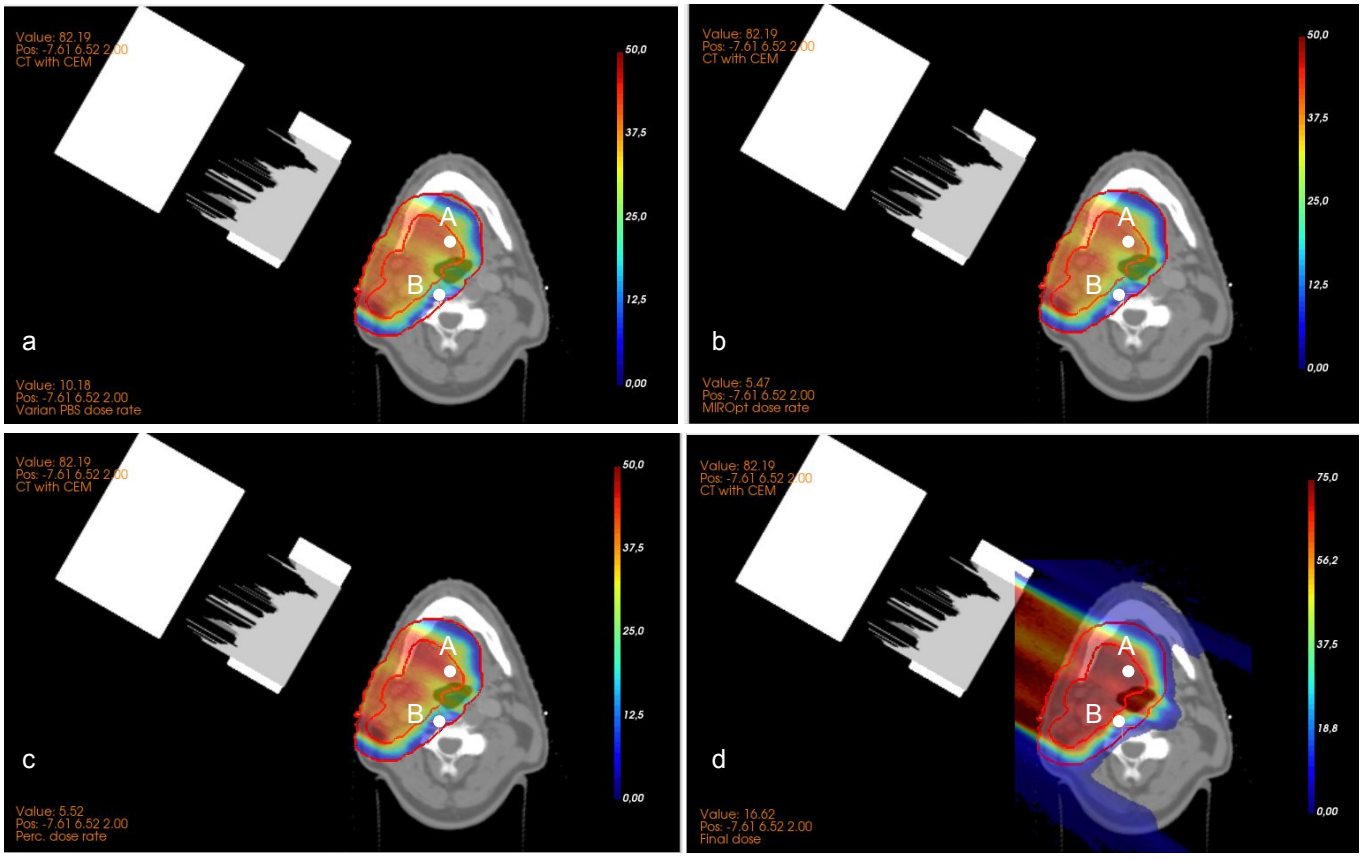

FIG. 3. (a) PBS (Varian) dose rate, (b) Relative threshold dose rate, (c) 95-percentile dose rate, and (d) dose map.

may impact the value of the computed dose rate by a factor of 2.

Naturally, the DADR leads to much higher dose rate values as periods which does not bring any contribution to the dose are discarded. As pointed out by others, this lack of consideration of the temporal structure of the dose delivery may provide the same dose rate estimate from an array of spots regardless of the delivery pattern and the time separating the spots[15]. In fact, by strictly conforming to this definition, the switching time between the energy layers of an IMPT is not an issue and the use of a range modulator is not necessary, which goes against what seems to be a consensus in the treatment planning community. However, as pointed out by Rothwell *et. al.*,

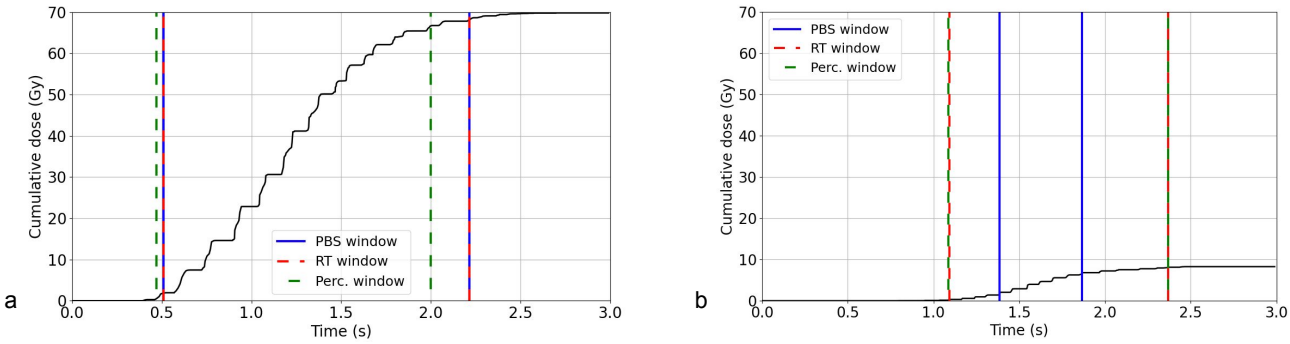

FIG. 4. Accumulated dose and time windows used by each one of the 'percentile type dose rates' for (a) point A and (b) point B defined in Fig. 3.

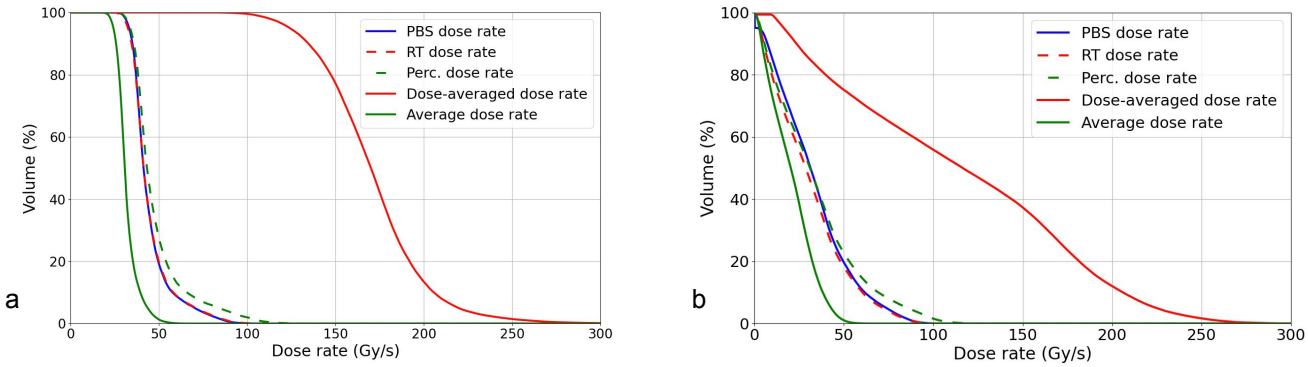

FIG. 5. DRVHs computed (a) on the PTV, and (b) on the PTV-ext.

the relevant time scale of the dose rate is still unknown as it is intrinsically related to the biology[14]. Given the lack of certainty regarding our understanding of the underlying mechanism of the FLASH effect, we cannot theoretically demonstrate which definition of the dose rate is more suitable. FLASH therapy is still an experimental method under evaluation and more experimental data are needed to determine which definition of dose rate is the most adequate.

This uncertainty should lead us to be cautious about the use of one definition or another. For example, the PBS dose rate, the RT dose rate, and the percentile dose rate are seemingly very close definitions. However, the corresponding dose rate values may vary locally on the order of 10%. These variations can also be seen in the DRVHs. In the *in silico* assessment, we had a DR95 of 5.41 Gy/s for the PBS dose rate and of 3.76 Gy/s for the percentile dose rate in PTV-ext whereas, in the PTV, the percentile dose rate was higher than the PBS dose rate. The differences are even more striking when looking at the DR5, where the three definitions lead to very different dose rate values.

Behind these three definitions are two fundamental questions:

- Is there a certain amount of dose that can be neglected in the dose rate calculation? If so, can this quantity be assimilated to a fixed value (PBS dose rate) or a percentage of the delivered dose (percentile dose rate, RT dose rate)?
- Does the time window depend on the exact moment at which the dose threshold mentioned above is reached (PBS dose rate, RT dose rate)? For example, if the threshold is set at 1 Gy, should we consider a time window between the moment when the dose reaches 0.5 Gy and the moment when it reaches dose-0.5 Gy? Or, on the contrary, if the threshold is set at 1 Gy, could we also consider a window starting when the dose reaches 0.2 Gy and ending when the dose is dose-0.8 Gy (percentile dose rate)?

The first question clearly relies on biolgical data and models. The second question may seem secondary. However, we have observed that locally the dose rate percentile can be more than 10% higher than the RT dose rate evaluated with the same relative threshold. This shows how necessary it is to define exactly what this threshold corresponds to, again through a cross-disciplinary approach.

V. CONCLUSIONS

Several definitions of the dose rate have been established, which mainly differ in the way that they take into account the spatial and temporal distributions of the PBS spots in proton therapy. In this paper, we have shown that this can lead to differences in the computed dose rate values varying from several percents up to a factor 2. As the dose rate is the key parameter in FLASH, the choice of the definition is very important. However, given the current uncertainty on the time scale related to the FLASH effect, we cannot currently determine which definition is the most suitable.

VI. ACKNOWLEDGMENTS

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VII. CONFLICT OF INTEREST STATEMENT

Dr. Valentin Hamaide was an employee of Ion Beam Applications during the writing of this paper.

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