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# Optimization of Alanine Measurements for Fast and Accurate Dosimetry in FLASH Radiation Therapy

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**Gondré, M., Gonçalves Jorge, P., Vozenin, M-C., Bourhis, J., Bochud, F., Bailat, C. and Moeckli, R. Optimization of Alanine Measurements for Fast and Accurate Dosimetry in FLASH Radiation Therapy. *Radiat. Res.* 194, 573–579 (2020).**

**FLASH radiation therapy (FLASH-RT) reference dosimetry to obtain traceability, repeatability and stability of irradiations cannot be performed with conventional dosimetric methods, such as monitor chambers or ionization chambers. Until now, only passive dosimeters have provided the necessary dosimetric data. Alanine dosimetry is accurate; however, to be used for FLASH-RT in biological experiments and for clinical transfer to humans, the reading time needs to be reduced, while preserving a maximum deviation to the reference of ±2%. Optimization of alanine dosimetry was based on the acquisition of electron paramagnetic resonance (EPR) spectra with a Bruker spectrometer. Reading parameters such as the conversion time, the number of scans, the time constant, the microwave power and the modulation amplitude of the magnetic field were optimized as a trade-off between the signal-to-noise ratio (SNR) and the reading time of one measurement using the reference 10.1 Gy alanine pellet. After optimizing the parameters, we compared the doses measured with alanine pellets up to 100 Gy with the reference doses, and then determined the number of measurements necessary to get a difference lower than ±2%. A low-dose alanine pellet of 4.9 Gy was also measured to evaluate the quality of the optimization for doses lower than 10 Gy. The optimization of the Bruker default parameters made it possible to reduce the reading time for one measurement from 5.6 to 2.6 min. That reduction was not at the cost of the SNR because it was kept comparable to the default parameters. Three measurements were enough to obtain a maximum dose deviation to the reference of 1.8% for the range of 10–100 Gy. The total reading time for the three measurements was 7.8 min (3 × 2.6 min). For lower doses such as 4.9 Gy, three measurements led to a deviation greater than 5%. By increasing the number of measurements to five, the average difference to the reference dose was reduced to less than 5% with a total reading time increased to 13.0 min. For doses between 10 Gy and 100 Gy, the optimized acquisition parameters made it possible to keep the average differences between the reference and the measured doses below ±2%, for a reading time of 7.8 min. This enabled an accurate and fast dose determination for biological preparations as part of FLASH-beam irradiations.** © 2020 by Radiation Research Society

## INTRODUCTION

FLASH radiation therapy (FLASH-RT), a novel technique incorporating ultra-high dose-rate (*2*), was recently used for the first time in humans (*3*). Interest in FLASH-RT is based on the resulting enhanced differential effect between normal tissues and tumors, which ultimately widens the therapeutic index (*4, 5*). At such high-dose rates, ionization chambers experience saturation effects (*6*). However, biological pre-clinical irradiations, as well as the transfer to humans (*7*), requires an accurate and repeatable dosimetry. Passive dosimeters such as alanine, thermoluminescent (TLD) and Gafchromic™ films are suitable, as they are independent of the dose rate (*8*). However, they require a significant time window between the irradiation and the dosimeter readout. Furthermore, the eRT6 linear accelerator was proven to have non-negligible day-to-day variations of the beam output in the FLASH irradiation mode (*2*). Therefore, dosimetric preparations with passive dosimeters are necessary just before biological experiments with animals or for patient treatments in the future. TLDs have an uncertainty level that cannot be further optimized, and film dosimetry typically requires 24 h of stabilization before reading. For these reasons, we focused on the optimization of alanine dosimetry, which could combine both high accuracy and short reading time. Optimization of alanine dosimetry was based on the acquisition of electron paramagnetic resonance (EPR) spectra with a Bruker spectrometer (*1*). Alanine dosimetry relies on the Zeeman effect, which leads to a splitting of the energetic levels when an external magnetic field is applied. In the case of electrons, two levels are created with spin magnetic moment of $m_s = \pm ½$. The difference in energy between the two levels is proportional to the external magnetic field applied.

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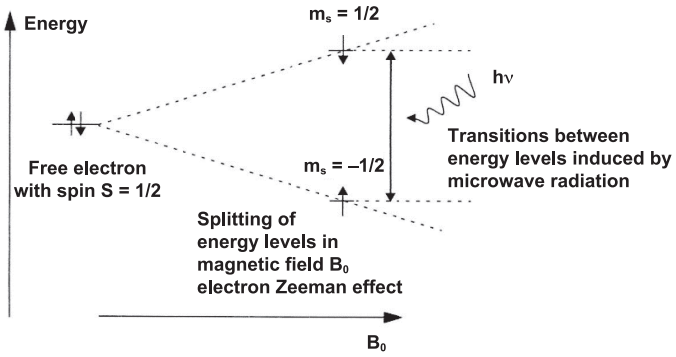


**FIG. 1.** Zeeman effect is described by a splitting of energetic levels when applying an external magnetic field $B_0$. In the case of an electron, two energetic levels are created with a difference of energy depending on $B_0$. An electron can change energetic level by absorption of a photon with corresponding energy hν.

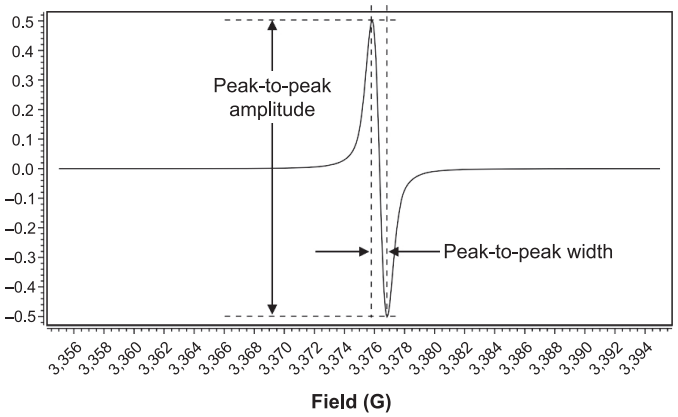


**FIG. 2.** EPR spectrum with corresponding peak-to-peak amplitude and width.

If a photon is sent with an energy corresponding to the difference in energy, the electron is absorbed to the excited state (see Fig. 1) (*9*). For the resonance condition to be met, either the external magnetic field or the photon energy can be varied. For EPR dosimetry, the energy of photons is kept fixed and the external magnetic field is varied. The EPR signal is obtained by the absorption of the unpaired electron to the higher energetic level. When an alanine pellet is irradiated, stable radicals with unpaired electrons are created in proportion with the dose. By applying a magnetic field and a constant photon frequency, the unpaired electrons are absorbed to the higher energetic level and an absorption spectrum is acquired. To increase the signal intensity, the magnetic field is modulated and therefore, it is the derivative of the absorption spectrum, which is recorded and referred to as the EPR spectrum. The EPR spectrum is characterized by its peak-to-peak amplitude and width (e.g., Fig. 2) (*1*). Therefore, by integrating the EPR spectrum, the absorption spectrum is obtained. The integration of the absorption spectrum gives the number of radicals created when the alanine pellet is irradiated, which is proportional to the dose. Alanine is tissue equivalent and shows no energy dependence within the therapeutic range (*10*). Additionally, no fading is observed for low-linear energy transfer (LET) radiation and for doses below $10^4$ Gy (*11*). Alanine dosimetry relies on the principle of EPR spectroscopy. The measurement process to achieve high dose accuracy can be time consuming. Therefore, we performed a joint optimization of the reading time and the SNR by optimizing the acquisition parameters to determine the dose more quickly while maintaining a high accuracy.

## MATERIALS AND METHODS

For our optimization, we used the WinEPR acquisition program available with the Bruker e-scan EPR spectrometer (Bremen, Germany), and a calibrated alanine pellet (4.9-mm diameter and 3.0-mm thickness) of 10.1 Gy (provided by Bruker). The optimization was performed over one measurement, which consisted of an average over a pre-defined number of spectra (the number of averaged spectra is defined as the number of scans in the WinEPR software). The WinEPR software made it possible to modify acquisition parameters, listed in Table 3, and to obtain EPR spectra. An EPR spectrum consists of the derivative of the absorption spectrum $A$ versus the magnetic field $B$ ($dA/dB$) as y-axis, and the magnetic field $B$ as x-axis. Several parameters could be modified. Some were linked both to the reading time and the SNR, like the conversion time, which represents the time spent on a point for the analog-to-digital conversion, and the number of scans, which enabled an average over several EPR-spectra. The time constant, the modulation amplitude of the magnetic field, and the microwave power, influence the SNR. Here, we investigated the possible influence of these parameters on the reading time. The time constant, which is related to the response time of the spectrometer, reduces noise caused by high frequencies by decreasing the response time of the spectrometer. The modulation of the magnetic field makes it possible to obtain the first derivative of the absorption spectrum and to increase the peak-to-peak amplitude of the signal. Additionally, the EPR signal increases linearly with the square root of the microwave power. For all these parameters, a trade-off is needed between the increase of signal amplitude and the loss of information due to distortion or saturation of the signal. Each parameter was optimized by keeping all other parameters fixed and varying one parameter at a time. The fixed parameter values for one measurement were a time constant of 20.48 ms, a conversion time of 5.1 ms, an average over 60 scans, a modulation amplitude of 0.32 mT and a power of 6.2 mW. We optimized each parameter according to the SNR determination and a time constraint: the objective was to keep at least a comparable SNR with respect to the initial Bruker parameters, while keeping the reading time for one measurement less than 3 min. The reading time for one measurement with the Bruker default parameters was 5.6 min. The SNR was calculated as the peak-to-peak amplitude of an internal reference signal, and the noise as the standard deviation of a nonirradiated alanine pellet. After optimizing the parameters, the reference alanine pellets of 10.1, 15.0, 19.9, 30.0, 50.1 and 100 Gy provided by Bruker were measured five times (5× the number of scan sets in the WinEPR program), and the mean dose over these five measurements was calculated and compared with the reference dose. The result was presented as a relative deviation to the reference dose (reference dose minus the mean measured dose divided by the reference dose). The repeatability property of consecutive measurements was assessed by measuring the reference 10.1 Gy alanine pellet an arbitrary number of times and by calculating the standard deviation. The stability of consecutive measurements could allow further reduction in the reading time by decreasing the total number of measurements. We then measured all alanine pellets three times. We compared the mean dose and standard deviation with those obtained with five measurements to determine if three measurements were

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**TABLE 1**
**Configurations of Conversion Time and Number of Scans Leading to a Measurement Process of Less than 3 Min**

| Conversion time (ms) | Number of scans | Configuration number |
|---|---|---|
| 1.28 | 273 | 1 |
| 2.56 | 140 | 2 |
| 5.12 | 60 | 3 |
| 10.24 | 34 | 4 |
| 20.48 | 17 | 5 |

enough to obtain a good dose accuracy. We also measured a low-dose (4.9 Gy) alanine pellet to evaluate the performance of the spectrometer for doses lower than 10 Gy.

*Time Constant Optimization*

The time constant makes it possible to reduce the noise caused by high frequencies. However, an excessive time constant leads to a distortion and a diminution of the signal. Therefore, we chose the time constant as a trade-off between noise reduction and the loss of signal. The optimal time constant is the highest time constant (leading to the highest SNR) before signal distortion. The tested time constant values were 0.32, 1.28, 5.12, 20.5, 81.9, 327.7, 1,311 and 5,245 ms.

*Microwave Power Optimization*

The EPR signal increases linearly as the square root of the microwave power. If the power is too high, saturation occurs and the relationship is not linear anymore. We increased the microwave power from 2 to 12 mW in increments of 2 mW to determine when saturation occurred. The optimal power was defined as the highest power before saturation.

*Modulation Amplitude Optimization*

The signal is initially obtained through the absorption of an unpaired electron from one energetic state to the other. The modulation of the magnetic field transforms the absorption signal to a sine wave (EPR spectrum). The amplitude of the sine is proportional to the slope of the absorption signal. When modulation amplitude is increased, the amplitude of the EPR signal is also increased. However, if the amplitude is too large, the signal is distorted and information is lost. We gradually increased the modulation amplitude (0.056, 0.1, 0.2, 0.32, 0.4 0.51, 0.63 and 0.71 mT) to determine the highest modulation amplitude that did not distort the EPR signals.

*Optimizing Conversion Time and Number of Scans*

The conversion time influences both the SNR and the reading time. It represents the amount of time needed by the analog-to-digital converter to integrate a field position before moving to the next position. A longer digitalization time means a less noisy signal but also a longer reading time, as it is directly related to the sweep time. We tested several conversion times (0.32, 1.28, 2.56, 5.12, 10.24 and 20.48 ms). The number of scans corresponds to the number of EPR spectra averaged during one measurement, and influences both the SNR and the reading time. Increasing the number of scans makes it possible to average over more scans and therefore, to reduce the noise. However, doubling the number of scans doubles the reading time. To fulfill a time constraint of 3 min for one measurement while enhancing the SNR, we selected the number of scans in accordance with the conversion time. We tested several combinations summarized in Table 1. As expected, when the conversion time increased, the number of scans required to fulfill the 3-min reading time condition decreased.

*Average Dose Deviation to the Reference*

After optimizing the parameters, we measured all reference alanine pellets provided by Bruker with 10.1, 15.0, 19.9, 30.0, 50.1 and 100 Gy doses to validate that the optimization was adequate up to 100 Gy. Additionally, we evaluated the number of measurements needed to obtain a deviation to the reference dose of less than $\pm 2\%$. Each pellet was measured five times (therefore, five times the chosen number of scans). Then we calculated the mean dose and compared it with the reference dose. The repeatability of the measurements was analyzed by measuring the 10.1 Gy alanine pellet several times (34 independent measurements) and by calculating the standard deviation. We then measured all alanine pellets three times. To verify whether we could reduce the reading time, we compared the deviation to the reference dose obtained with three measurements to the one obtained with five measurements.

*Comparing EPR Signals Between Bruker Default Parameters and Optimized Parameters*

To evaluate the gain obtained with the optimization, we recorded the EPR spectra with the 10.1 Gy alanine pellet using the Bruker default parameters and the optimized ones. The SNR was calculated for both spectra and compared.

*Low-Dose Measurement*

According to Bruker Inc., the EPR dosimeter reader is accurate from 10 Gy to 200 kGy (*12*). This means that a dose such as 4.9 Gy is challenging for a spectrometric measurement even if it is a realistic possible measurement in radiation therapy. For such low doses, a longer reading time can be necessary to obtain a lower difference between the reference dose and the mean measured dose. We measured a 4.9 Gy reference alanine pellet and calculated the mean deviation to the reference dose. We then determined the mean dose for three and five measurements.

## RESULTS

*Time Constant Optimization*

Figure 3 shows the influence of the time constant on EPR spectra. Figure 3A shows the EPR signals for a subset of studied time constants: 1.28, 20.48 and 327.68 ms. The signal with a time constant of 327.68 ms is distorted. The spectra with the time constant of 1.28 and 20.48 ms are superimposed, but the noise is clearly less for a time constant of 20.48 ms compared to 1.28 ms, as shown in Fig. 3B.

*Microwave Power Optimization*

As indicated by the black filled line in Fig. 4, a saturation occurs above the square root of the power equal to 2.493 $mW^{1/2}$. Therefore, the optimal power, leading to the highest peak-to-peak amplitude with no saturation, corresponded to 6.215 mW.

*Modulation Amplitude Optimization*

Figure 5 shows the effect of the increase of the modulation amplitude of the magnetic field. In Fig. 5A a subset of tested amplitudes are represented: 0.1, 0.2, 0.32 and 0.71 mT. When increasing the modulation amplitude,

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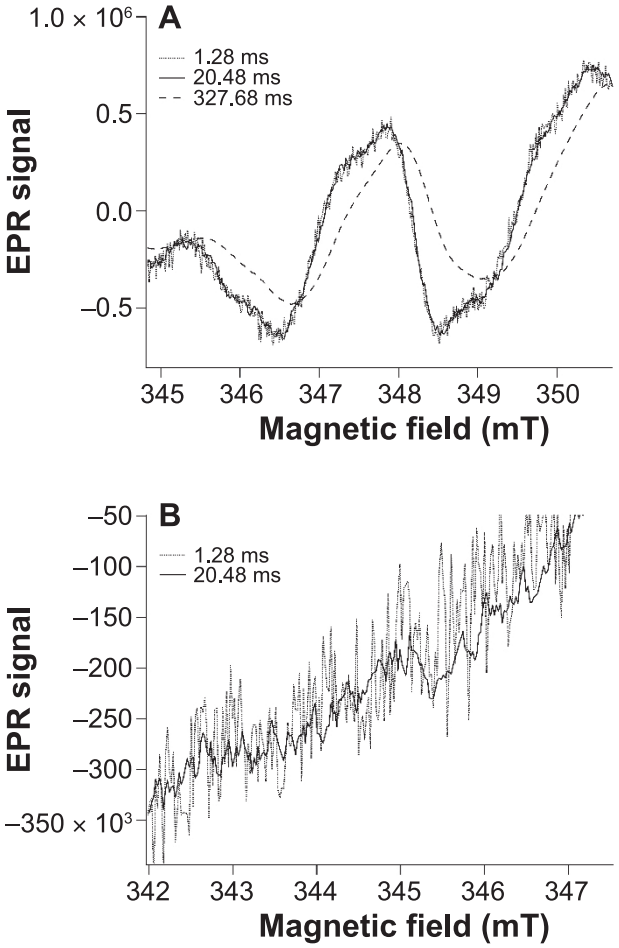


**FIG. 3.** Time constant influence on EPR spectra. Panel A: EPR signals for a time constant of 1.28 ms (dotted line), 20.48 ms (filled line) and 327.68 ms (dashed line). Panel B: Magnification of Fig. 3A for noise comparison between a time constant of 1.28 ms (dotted line) and 20.48 ms (filled line).

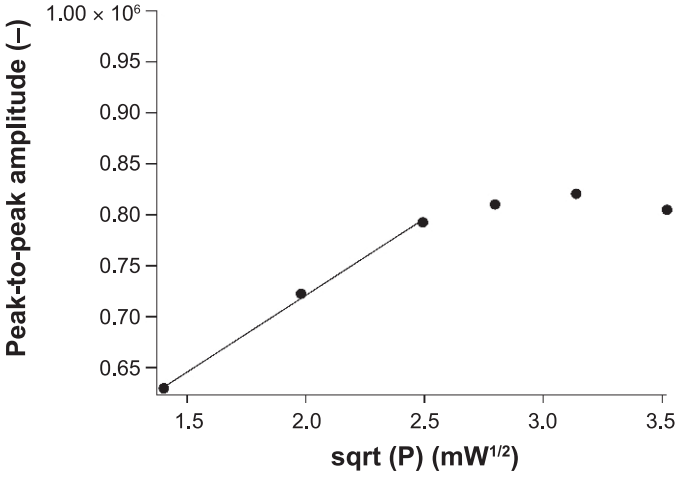


**FIG. 4.** The peak-to-peak amplitude is represented as a function of the square root of the power. Saturation occurs from a power of 6.215 mW. The black filled line is a linear fit between the peak-to-peak amplitude and the square root of the power for power less or equal to 6.215 mW.

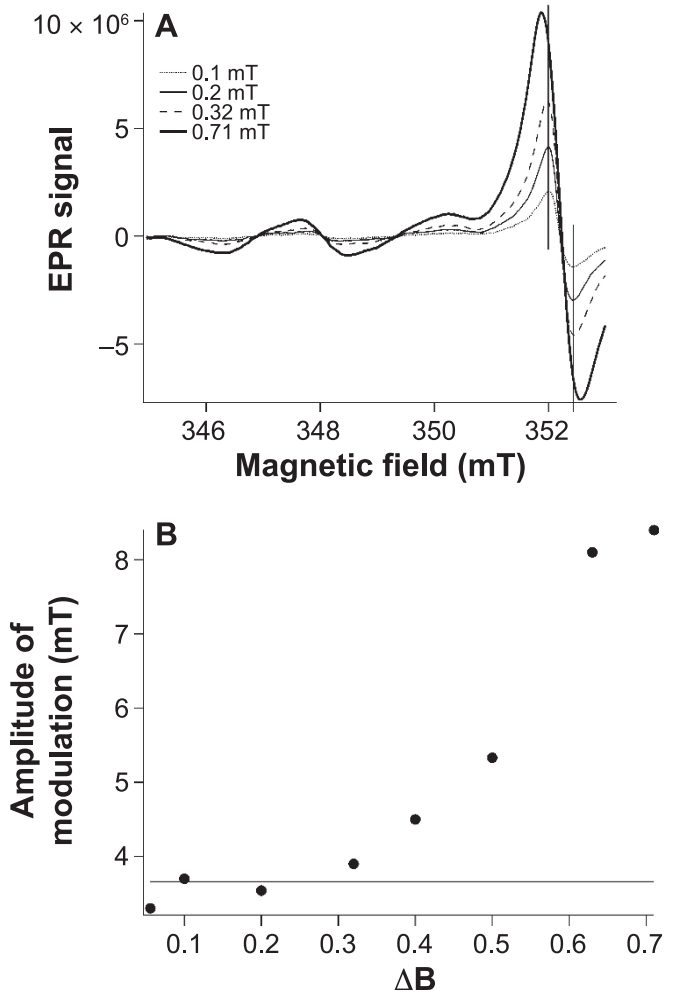


**FIG. 5.** Effect of the modulation amplitude on the EPR signals. Panel A: EPR signal for four amplitudes: 0.1 mT (dotted line), 0.2 mT (filled line), 0.32 mT (dashed line) and 0.71 mT (bold line). The vertical lines show the peak shift for 0.71 mT. Panel B: Peak-to-peak width on x-axis as a function of the modulation amplitude. Above 0.32 mT, the width between the peaks increases due to the distortion, as highlighted by the horizontal line.

the peak-to-peak amplitude increases. However, for the 0.71-mT amplitude the peak is shifted on the x-axis, while the peaks for the 0.1, 0.2 and 0.32 mT are aligned (vertical lines in Fig. 5A). Figure 5B represents the modulation amplitude as a function of the peak-to-peak width. The width is constant for the 0.056, 0.1, 0.2 and 0.32 mT and increases above that. Therefore, the optimal amplitude modulation was 0.32 mT.

### *Conversion Time and Number of Scans Optimization*

When increasing the conversion time (with a constant number of scans), the amplitude of the signal increases. However, when the conversion time was too low, e.g., for 0.32 ms and 1.28 ms, the signal was distorted. Therefore, the minimum conversion time was 5.12 ms. However, when increasing the conversion time, the reading time was also drastically increased. We also performed a joint optimization

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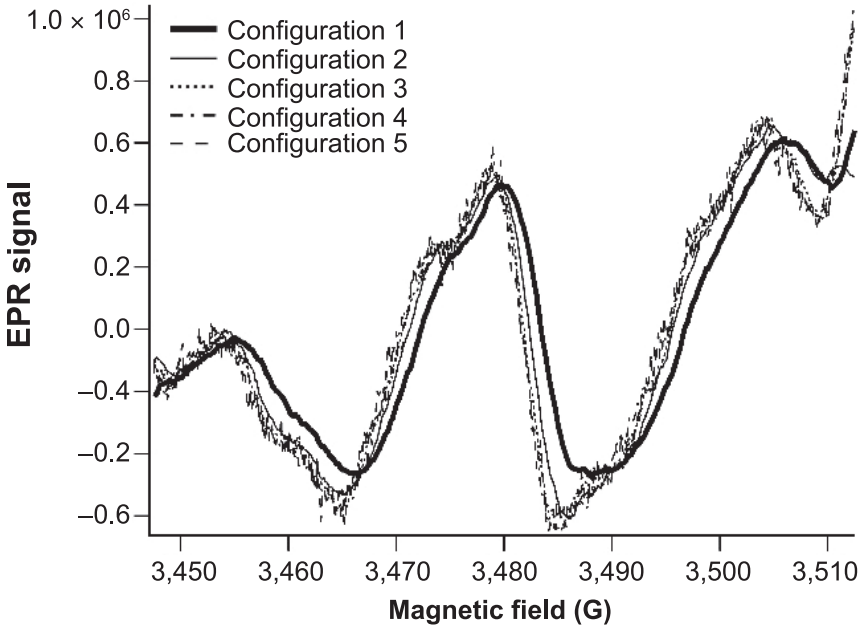


**FIG. 6.** Joint optimization of the conversion time and the number of scans. All five configurations (see Table 1) lead to a reading time of less than 3 min.

of the conversion time and the number of scans through five configurations of conversion time and number of scans leading to the same reading time of approximately 3 min (Fig. 6). For low conversion time, e.g., configuration numbers 1 and 2, the signals were distorted, as previously mentioned. The other three configurations led to the same amplitude. However, the configuration leading to the least noisy signal was configuration number 3, which corresponded to a conversion time of 5.12 ms and an average over 60 scans.

### *Average Dose Deviations to the Reference of the Calibrated Alanine Pellets for a Range of 10.1–100 Gy*

We measured all the reference alanine pellets five times (5 × 60 scans) for a total reading time of 13.0 min. The deviation ran between –1.2% for 100 Gy and 1.9% for 30 Gy. We then tested the stability of the measurements by repeating the measurement of the 10.1 Gy alanine pellet 34 times. The standard deviation was 0.22 Gy. This meant that we could reduce the number of measurements to three, since the intrinsic uncertainty of the measurement was superior to the uncertainty related to the repetition of the measurement. All alanine pellets were then measured three times, leading to a reading time of 7.8 min. For this number of measurements, the deviation to the reference was between –1.3% and 1.8% (Table 2).

### *Comparing EPR Signals Between Bruker Default Parameters and Optimized Parameters*

Figure 7 shows the SNR evaluation performed on EPR spectra obtained with the Bruker default parameters and the optimized ones. For the Bruker parameters, the time needed to acquire the spectrum with one measurement was 5.6 min while the reading time was 2.6 min for the optimized parameters. As shown in Fig. 7A, the amplitude of the signal was higher for the EPR spectrum obtained with the optimized parameters. However, the noise was less important with the Bruker default parameters (Fig. 7B).

Table 3 provides a summary of the optimized parameters and the Bruker default parameters. The SNRs obtained using both Bruker default parameters and the optimized

**TABLE 2**
**Mean Measured Dose, Standard Deviation, and Deviation to the Reference Dose for Doses from 10.1 Gy to 100 Gy with Five and Three Measurements**

| | Mean measured dose (Gy) | | Standard deviation | | Deviation to reference dose (%) | |
|---|---|---|---|---|---|---|
| Reference dose (Gy) | 5 measurements | 3 measurements | 5 measurements | 3 measurements | 5 measurements | 3 measurements |
| 10.1 | 10.1 | 10.2 | 0.2 | 0.2 | 0.0 | 0.7 |
| 15.0 | 15.0 | 15.1 | 0.3 | 0.1 | –0.1 | 0.8 |
| 19.9 | 19.7 | 19.8 | 0.5 | 0.1 | –1.0 | –0.8 |
| 30 | 30.6 | 30.5 | 0.2 | 0.2 | 1.9 | 1.8 |
| 50.1 | 50.9 | 50.7 | 0.9 | 0.6 | 1.5 | 1.2 |
| 100 | 98.9 | 98.7 | 0.3 | 0.2 | –1.2 | –1.3 |

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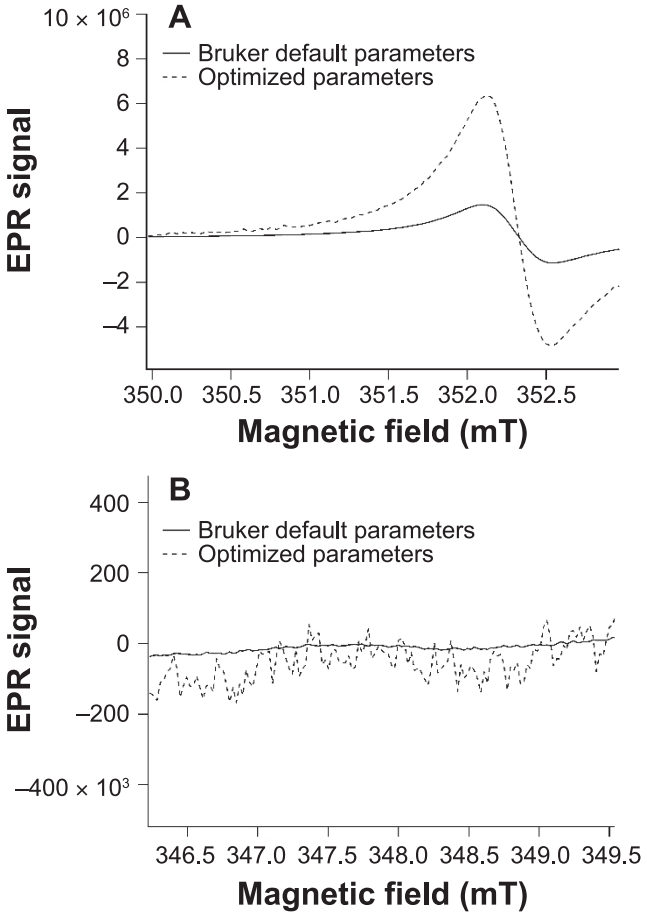


**FIG. 7.** SNR evaluation of the EPR spectra obtained with Bruker default parameters (filled line) and the optimized parameters (dashed line). Panel A: EPR spectra. Panel B: Noise comparison.

parameters were high. Regarding these high SNRs, they were considered as comparable. However, the measurement was performed in 2.6 min with the optimized parameters and in 5.6 min with the Bruker parameters.

*Low Dose: 4.9 Gy*

The mean measured dose obtained with three measurements was 4.6 Gy, leading to a deviation from the reference of –5.5%. When increasing the reading time to five measurements, the deviation to the reference was lowered to –5.0%.

**TABLE 3**
**Summary of Bruker Default Parameters and Optimized Parameters, Comparison of Reading Time and SNR**

| Parameters | Bruker default parameters | Optimized parameters |
|---|---|---|
| Time constant (ms) | 5.12 | 20.48 |
| Conversion time (ms) | 5.12 | 5.12 |
| Number of scans | 128 | 60 |
| Modulation amplitude (mT) | 0.4 | 0.32 |
| Microwave power (mW) | 12.4 | 6.22 |
| Reading time (min) | 5.6 | 2.6 |
| SNR | 93.8 | 98.8 |

## DISCUSSION

In this study, we were able to minimize the reading time of the alanine pellet while keeping an equivalent SNR by optimizing the reading parameters.

While the time constant, power and modulation amplitude were shown to have an impact on the SNR, after optimization it appeared that they did not influence the reading time. Therefore, the SNR could be maximized by optimizing these three parameters without increasing the reading time. However, the increase of SNR was balanced with the distortion of the signals or saturation. By increasing the time constant, the noise caused by high frequencies was filtered out. However, above a certain threshold, the signal itself was excessively filtered and the dose information was lost. When power was increased, the signal amplitude also increased, but saturation occurred for powers above 6.22 mW. Increasing the modulation amplitude made it possible to increase the peak-to-peak amplitude on the EPR spectra. However, above a certain amplitude, the peaks were shifted to the left for the upper peak and to the right for the lower peak. The signal was thus enlarged and the information about the absorption of unpaired electron to higher energetic level was compromised. Therefore, the highest amplitude before distortion was the optimized one. The conversion time and the number of scans had an opposite effect on the SNR and the reading time. They were defined by finding the best SNR achievable with one measurement of less than 3 min.

After having defined the optimized parameters (summarized in Table 3), we evaluated the number of measurements necessary to obtain a deviation less than ±2%. We measured all alanine pellets five times for a reading time of 13.0 min and the deviations to the reference were all below ±2% (maximum 1.9%).

To evaluate the stability of the measurements, and possibly to reduce the reading time, we measured the 10.1 Gy alanine pellet several times (i.e., a total of 34 times). The standard deviation obtained with 34 measurements (0.22 Gy) was greater than the standard deviations obtained with three and five measurements (0.19 Gy). This indicates that the number of measurements did not have a crucial impact on the uncertainty because it was the intrinsic uncertainty of the measurement which had the dominant effect. Therefore, the number of measurements could be reduced from five to three, with all deviations to the reference still less than ±2% (maximum 1.8%). The deviations to reference dose were found to be similar between five and three measurements for doses from 19.9 Gy to 100 Gy, indicating the possibility of reducing the reading time without loss of accuracy. For the 10.1 and 15.0 Gy doses, the deviations were larger for three measurements, but still reasonable. The total reading time was thus reduced to 7.8 min. We chose not to further decrease the number of measurements, to be able to discriminate outliers in the measurements.

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For low doses, a reading time of 7.8 min did not make it possible to obtain a mean deviation to the reference dose lower than ±5%. Therefore, to increase the accuracy for such low doses, the reading time was increased to five measurements performed over 13.0 min, with a deviation lower than ±5%.

Finally, the comparison was made between spectra obtained after one measurement with the Bruker default parameters and with the optimized parameters using the 10.1 Gy alanine pellet. The SNR of the optimized parameters was 98.8 and the SNR of the default parameters was 93.8. The spectrum was acquired in 5.6 min for the default parameters and in 2.6 min for the new ones. Therefore, due to the optimization, the SNR was on the same order as before but with a reading time more than twice as fast. A deviation to the reference of less than ±2% in 2.6 min was considered a good trade-off for the use of alanine.

In a published study, the eRT6 linear accelerator was shown to have a good short-term stability (deviation smaller than 1% for ten consecutive measurements), but non-negligible day-to-day variations of the beam output were observed (*2*). These day-to-day variations led to a loss of dose accuracy. Reducing the alanine reading time meant that we could measure just before the irradiation of animals as well as obtain the resulting dose just before the irradiation. This led to a better precision of the dose delivered to animals in pre-clinical studies. For the transfer of FLASH-RT to human, optimizing the reading parameters will make a rapid *in vivo* dose measurement possible prior to the irradiation, ensuring better safety for the patient. Therefore, the fast reading time of the EPR spectrometer combined with high dose accuracy will ensure optimal radiotherapy of patients.

## CONCLUSION

We were able to optimize the EPR spectrometer's acquisition parameters in the range of 10.1–100 Gy to obtain an accurate dose determination with a maximum deviation to the reference of ±2%, for a total reading time of 7.8 min. This high accuracy combined with a fast detection method enables alanine to be used as the reference dosimeter for FLASH-RT, providing traceability, repeatability and stability of irradiations. For doses lower than 10 Gy, the analysis of the 4.9 Gy reference alanine pellet showed a deviation to the reference of less than ±5% for a reading time of 13.0 min.

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