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Vasi, Fabiano ; Schneider, Uwe

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First Measurements of Ionization Cluster-Size Distributions with a Compact Nanodosimeter

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Abstract

Purpose: A nanodosimeter is a type of detector which measures single ionizations in a small gaseous volume in order to obtain ionization cluster size probability distributions for characterization of radiation types. Working nanodosimeter detectors are usually bulky machines which require a lot of space. In this work, the authors present a compact ceramic nanodosimeter detector and report on first measurements of cluster size distributions of 5 MeV alpha particles.

Methods: Single ionization measurements are achieved by applying a weak electric field to collect positive ions in a hole in a ceramic plate. Inside the ceramic plate, due to a strong electric field, the ions are accelerated and produce impact-ionizations. The resulting electron avalanche is detected in a read-out electrode. A bayesian unfolding algorithm is then applied to the experimentally obtained cluster size distributions to reconstruct the true cluster size distributions.

Results: Experimentally obtained cluster size distributions by the compact nanodosimeter detector are presented. The reconstructed cluster size distributions agreed well with Monte Carlo simulated cluster size distributions for small volumes (diameter = 2.5 nm). For larger volumes discrepancies between the reconstructed cluster size distributions and cluster size distributions from Monte Carlo simulations were observed.

Conclusions: For the first time ionization cluster size probability distributions could be obtained by a small and compact nanodosimeter detector. This signifies the achievement of a critical step towards the wide application of nanodosimetric characterization of radiation types including in clinical environments.

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1. Introduction

Biological effects produced by various types of ionizing radiation lack a consistent relation with absorbed dose. In order to still be able to apply the concept of the absorbed dose, the so-called relative biological effectiveness (RBE) was introduced. The aim of nanodosimetry is to provide physical measurements of a quantity which describes biological effects of ionizing radiation better than conventional absorbed dose measurements. A common fundamental cause of biological effects is the productions of double-strand breaks which correlate with the probability to produce ionizations within a volume of 10 base pairs of DNA.¹²³⁴ The nanodosimetric quantity, which is measured in a DNA-sized volume, is the number of ionizations ν produced by single traversing charged particles of specified radiation quality, which is described by a probability distribution $P(\nu)$.

The application of nanodosimetric information in treatment plans is an active research area. Two different strategies for treatment plan optimization using nanodosimetric parameters to quantify the biological effects in the patient were proposed by Casiraghi et al for proton and carbon ion radiotherapy.⁵ Alexander et al. presented a track structure parametrization for protons and carbon ions in the energy range used clinically. In combination with a stopping power weighted method the parametrization can be used to characterize the track structure of a mixed radiation field.⁶⁷ Conte et al. were able to establish a relationship between nanodosimetric quantities and the coefficients of the linear-quadratic model.⁸ The relative biological effectiveness can then be derived from the obtained linear-quadratic model parameters. Ramos-Méndez et al. investigated the distribution of nanodosimetric quantities in IMPT plans for protons and carbon ions.⁹ The simultaneous optimization of RBE-weighted dose and nanodosimetric quantities in carbon-ion treatment plans was proposed by Burigo et al.¹⁰ A model of radiation action based on nanodosimetric quantities has been developed by Besserer and Schneider.¹¹¹²¹³¹⁴ It was postulated that biological effects are caused by the production of elementary sublesions (DSBs) which are proportional to the nanodosimetric cumulative probability to create at least two ionizations. An expression for the relative biological effectiveness was derived and theoretical results were compared to experimental RBE-values. In summary, nanodosimetry could currently yield the best approximation of the RBE with a physical measurement.

Most current nanodosimeter detectors are large and bulky machines.¹⁵¹⁶¹⁷¹⁸ To make nan-

odosimetry practically usable it is necessary to develop a compact and portable nanodosimeter. Several attempts have been made for downsizing nanodosimeters.^{19 20} Although with the new compact detector design single ionizations could be measured, it was not yet possible to measure complete cluster size distributions.²¹ Here we report on first measurements of cluster size distributions of 5 MeV alpha particles with a ceramic nanodosimeter detector.

II. Methods

II.A. Detector Set-up

The detector is composed of a ceramic plate with one hole in the middle which is inserted into the lid of a low pressure chamber (see a sketch of the set-up in figure 1 and a picture from inside the chamber in figure 2). The ceramic consists of zirconium oxide (ZrO_2) doped with Yttrium oxide (Y_2O_3) and has a resistivity in the order of $10^{10} \Omega \text{ cm}$ at room temperature (Ceramdis, Im Tubental 5, 8352 Elsau, Switzerland). The thickness of the ceramic plate was 10 mm and hence this was also the length of the hole channel. The diameter of the hole is 1.5 mm and the part of the ceramic disc facing the inside of the chamber has a diameter of 43.9 mm and the part facing outside the chamber has a disc diameter of 51.9 mm. A low-resistive silicate glass produced by Wang et al. with a bulk resistivity in the order of $10^{10} \Omega \text{ cm}$ was put on top of the ceramic plate.²² It was sealed with a silicon sealant. Carbon- and copper-tapes were put on top of the glass. A high voltage cable was soldered on to the top of the copper tape.

The bottom side of the ceramic plate was covered with two sections of copper tape. The first section, directly around the hole, functions as the readout electrode. The second section, around the first section, was connected to ground. The second section was attached to the bottom of the ceramic plate in order to avoid a distortion of the electric field lines (the first section is shown in figure 2 and the field lines are shown in figure 1).

Inside the low-pressure chamber, a collimated alpha particle source was placed 11 mm below the ceramic plate in order to produce ionizations inside the sensitive volume. The maximal beam diameter below the center of the hole is 2.6 mm. The alpha particle source is made of americium-241 which is incorporated into a thin gold layer. The maximum energy of the alpha particles was approximately 4.7 MeV after the self absorption of the gold matrix and

the activity of the source was $11.1 \text{ MBq} \pm 3.3 \text{ MBq}$. Moreover, a copper anode was placed 22 mm below the ceramic plate and its voltage was set to 10 V. The voltage on top of the glass cathode was set to -1500 V . The resulting potentials and shapes of the electric field lines are shown in figure 1. A surface barrier detector with an active area of 25 mm^2 and a diameter of 5.64 mm was placed opposite to the alpha source. It detects all alpha particles which traversed through the drift volume below the hole in the ceramic plate (figure 1).

II.B. Detector Principle and Data Acquisition

The pressure of the propane gas is held constant inside the measuring chamber and was set to 266.6 Pa. The hole diameter in mass per area is $0.72 \mu\text{g cm}^{-2}$ or 7.2 nm when scaled at unit density. The low pressure allows to measure cluster size distributions in millimetric instead of nanometric dimensions because the sensitive volume scales with the density ratio to nanometric dimensions in liquid water. Biological tissue consists to a large extent of water and therefore liquid water is often used as a surrogate for tissue. Propane gas was used as the experimental medium because it has been shown that in propane the shape of the mean free path for primary ionizations as a function of particle velocity is similar to that in liquid water; the cluster size distributions simulated in the two materials are similar if the propane mass-thickness is reduced by a factor 0.8 with respect to the water thickness.²³

The working principle of the detector is based on the detection of single ions. Alpha particles traverse the sensitive volume below the hole and ionize propane molecules along their trajectory. The resulting positive ions in the sensitive volume drift due to the electric field to the hole of the ceramic plate, where they arrive at different times. Inside the hole the ions are accelerated by a strong electric field and produce ion-impact ionizations. Hence ion-electron pairs are created. The resulting electrons and ions are accelerated in opposite directions and produce even more ionizations. These charged particles also produce ionizations, and so on. Since the electrons weigh much less than the ionized propane molecules, they reach higher velocities and ionize the gas more strongly. This process leads to the development of an ionization avalanche which is registered by the readout electrode at the bottom of the ceramic plate. Because of the high electric field strength inside the hole channel, this avalanche process happens very quickly. Therefore, the ions produced in the sensitive volume, which slowly drift to the hole and arrive there at different times, ideally produce distinguishable

ionization avalanches.

The avalanches are limited in space by the ceramic walls and discharges are suppressed by the use of the silicate glass. The high bulk resistivity of the glass compared to a metal electrode is responsible for the accumulation of positive ions on the glass. This accumulation of positive charges shields the lower part of the hole from the high negative voltage of the cathode and in turn reduces the effective voltage inside the hole. Thus the resistive cathode allows a discharge-free operation of the nanodosimeter in the low-pressure gas.

When an alpha particle traverses the sensitive volume, it is absorbed by a silicon surface barrier detector, which triggers an acquisition window. The detected counts during the open acquisition window are stored electronically by a field programmable gate array (FPGA). The length of the acquisition gate was adapted to the drift times of the ions and set to 1 ms. The mean dark count per 1 ms is also determined which is defined as the number of registered ionization avalanches per 1 ms when no alpha particle traverses the sensitive volume. The dark count is randomly distributed in time. The mean dark count is subtracted from the obtained mean signal count in order to correct for background and noise signals.

II.C. Reconstruction of Cluster Size Distributions

The detector has an ion detection efficiency lower than 100% and thus clusters sizes ν are counted as μ ionizations, where $\mu \leq \nu$. Therefore, to obtain the true cluster size distribution from the measured cluster size distribution, the iterative bayesian unfolding method was applied. The method was implemented in the following way: Let ν_i ($i = 0, 1, 2, \dots, n_t$) be the true cluster sizes and μ_j ($j = 0, 1, 2, \dots, n_{exp}$) the measured cluster sizes at a detection efficiency ε . First a uniform initial probability distribution ($\mathbf{P}_0(\nu)$), was assumed and the length of ν was set to 100. The probability $P(\nu_i) = \sum_{j=0}^{n_{exp}} P(\mu_j)P(\nu_i | \mu_j)$ was calculated using Bayes' theorem:

$$P(\nu_i | \mu_j) = \frac{P(\mu_j | \nu_i)P_0(\nu_i)}{\sum_{l=0}^{n_t} P(\mu_j | \nu_l)P_0(\nu_l)} \quad (1)$$

$P(\mu_j | \nu_i)$ is given by the binomial probability distribution $B(j | i; \varepsilon) = \binom{i}{j} \varepsilon^j (1 - \varepsilon)^{(i-j)}$.

A χ^2 comparison based on the relative differences between $\mathbf{P}_0(\nu)$ and $\mathbf{P}(\nu)$ was made. If the value of χ^2 was lower than 0.01, the iteration was stopped. Otherwise $\mathbf{P}_0(\nu)$ was replaced by $\mathbf{P}(\nu)$ and the same procedure was repeated.

The efficiency ε of the detector is determined by comparing the mean cluster size M_1 from Monte Carlo simulations with the measured mean number of ions per alpha particle. For the Monte Carlo simulations of the cluster size distributions TOPAS was used with the Geant4-DNA extension (Geant4 version 10.02 patch 01). A monoenergetic point-source, positioned on the surface of a water sphere, was employed. The emitting direction of the particles was perpendicular to the sphere surface. The default physics constructor was used for liquid water. The diameters of the spherical sensitive volumes in water were chosen to be 2.5 nm, 5 nm, 7 nm and 10 nm. These diameters correspond to effective diameters of the spherical volumes in propane at unit density of about 2 nm, 4 nm, 6 nm and 8 nm, respectively.

Another method to compare the measured cluster size distributions with the Monte Carlo simulated cluster size distributions is a procedure opposite to what is described in the last paragraph. By applying a uniform efficiency, the expected cluster size distribution $P(\mu)$ can be calculated from the simulated Monte Carlo cluster size distribution using the binomial probability:

$$P(\mu | \varepsilon) = \sum_{\nu=\mu}^{\infty} \binom{\nu}{\mu} \varepsilon^{\mu} (1 - \varepsilon)^{\nu-\mu} P(\nu) \quad (2)$$

III. Results

In figure 3 the black squares represent the measured cluster size distributions and the blue circles represent the Bayesian reconstructed cluster size distributions. Moreover, the red triangles in figure 3 represent the Monte Carlo simulated cluster size distributions. The yellow diamonds represent the expected cluster size distribution $P(\mu)$ calculated from the simulated Monte Carlo cluster size distribution using the binomial probability according to equation 2.

Two experimental runs were carried out. The black squares in figure 3a show the measured cluster size distribution of the first experimental run at 2 Torr, an anode voltage of 10 V and an acceleration voltage of -1500 V. The mean number of ions per alpha particle obtained was 0.72 and the standard deviation was 0.06. In total 366 831 alpha particles were registered during this measurement run. The full width at half maximum of the signals was always smaller than 150 ns. The mean cluster size M_1 from Monte Carlo simulations in a sphere

with a diameter of 2.5 nm was 4.58 which results in an efficiency ε of 15.7%. In figure 3a, the diameter of the sphere used in the Monte Carlo simulations is 2.5 nm. The blue circles in figure 3a represent the reconstructed cluster size distributions with the calculated efficiency ε of 15.7%.

The ion detection efficiency ε is not constant for the detector and depends on temperature, detector ageing, and other unknown features. Therefore, a second independent experimental run is shown in figures 3b to 3d using the same experimental set-up properties.

The mean number of ions per alpha particle obtained in the second run was 0.91, which results in an efficiency ε of 19.9% assuming a sensitive sphere with a diameter of 2.5 nm. The corresponding cluster size distributions are shown in figure 3b.

If the diameter of the sensitive sphere is increased to 5 nm, then the mean cluster size M_1 of the Monte Carlo simulated distribution increases to 11.01. This results in a calculated ion detection efficiency ε of 8.3%. The corresponding cluster size distributions are shown in figure 3c.

If the diameter of the sensitive sphere is assumed to be 7 nm, the mean cluster size M_1 obtained in the Monte Carlo simulations is 16.89. This results in a calculated ion detection efficiency ε of 5.4%. The corresponding cluster size distributions are shown in figure 3d.

IV. Discussion

For the first time it was shown that a small and portable nanodosimeter detector has the potential to measure cluster size distributions.

Reconstructed cluster size distributions in nanometric volumes using the Bayesian unfolding algorithm agreed satisfactorily with cluster size distributions from Monte Carlo simulations.

The sensitive volume of the detector was estimated by simple pressure scaling. This resulted in an equivalent spherical sensitive volume of approximately 10 nm in diameter in water. Surprisingly, however, our results agree best with Monte Carlo simulations, assuming a diameter of 2.5 nm in water. The reason for this discrepancy could be that for increasing sensitive volumes the detection efficiencies are decreasing. Smaller detection efficiencies are related to an inferior reconstruction quality. The reconstruction of cluster size distributions in larger volumes can be improved by changing the Bayesian stopping criteria to allow a

larger number of iterations. Nevertheless, the quality of cluster size distributions of the 2.5 nm diameter volumes cannot be reached.

An investigation of the iteration stopping criteria of the Bayesian reconstruction method could be important to improve the reliability of the reconstructed cluster size distributions from measurements. The reconstruction of cluster size distributions is substantially based on the knowledge of the detector efficiency which was determined by Monte Carlo simulations. Uncertainties of the cross-sections and of transport models of Monte Carlo codes also increase the uncertainties of the reconstructed cluster size distributions.

The distribution $P_\nu(Binomial)$ obtained by using the binomial probability (Equation 2) together with distribution from the Monte Carlo simulations deviates from the measured distribution $P_\mu(Experiment)$. One possible explanation for this discrepancy is the assumption of a uniform efficiency over the sensitive volume which is independent of the cluster size. It is more realistic that the probability decreases outwards in the sensitive volume and a probability map could help to describe the sensitive volume more accurately. In addition, realistic detector efficiency depends on many parameters including the cluster size. Another reason for the observed difference could be that in the Monte Carlo simulations an infinite small pencil beam is simulated, whereas under the experimental conditions the beam size is finite. Moreover, several physical aspects such as ageing and the accumulation of charges on the walls and the cathode will influence the electric field inside the hole and the dead time and thus the response function and efficiency of the detector. The efficiency should be studied in more detail for future work. Since a simplified, uniform efficiency was taken into account, a greater uncertainty can be assumed.

A difference on the order of 25 % was recorded in the mean cluster size values for two independent experimental runs. Assuming different detector efficiencies, the two experimentally obtained cluster size probability distributions resulted in similar reconstructed probability distributions. Although cluster size distributions can be reconstructed from experimental runs with different detection efficiencies, it would be desirable to work with a detector of a constant and known efficiency. This would make the reconstruction procedure completely independent from information obtained by Monte Carlo simulations, e.g. here the knowledge of the mean ionization cluster size M_1 to estimate the efficiency. However, the independent measurement of detector efficiency is still an open problem.

Curiously, it was observed that in both experimentally obtained probability distributions,

the probability P_1 was greater than the probability P_0 . We can see from the binomial reconstructed probability distributions P_μ in figure 3 that this is not to be expected. In figure 3b, this phenomenon is observed when an efficiency of 19.9% is assumed and a diameter of 2.5 nm. It would be expected that P_1 is larger than P_0 only for diameters greater than 5 nm assuming an efficiency of 19.9%. Hence, this behavior is not understood yet and has to be investigated in the future.

The expected cluster size distributions at a certain efficiency calculated from Monte Carlo simulations using equation 2 differed from the experimentally obtained cluster size distributions in particular for greater efficiencies (15.7% and 19.9%). At these efficiencies, the measured probabilities for cluster sizes between 3 and 7 are smaller than the expected ones from Monte Carlo simulations. The reason for this discrepancy in cluster sizes 3 through 7 has to be investigated and could be a consequence of decreasing efficiency with increasing cluster size.

The cluster size distributions of densely ionizing particles are strongly dependent on the diameter of the target volume, and therefore the difference between cluster size distributions in cylindrical and spherical volumes of the same diameter is negligible. Spherical sensitive volumes have the advantage of being independent of the direction of the incident particle. With respect to the use of cluster size distributions in modelling biological damages, cell survival or the relative biological effectiveness, such as in a nanodosimetric radiation action model¹, spherical volumes are preferred. In addition, spherical volumes are also preferred when Monte Carlo methods are used to obtain cluster size distributions (or parameters derived from the cluster size distribution) in macroscopic volumes for optimizing treatment plans (for an example see Vasi et al.²⁹). With such applications in mind and the negligible difference between spheres and cylinders, we decided to assume the sensitive volume is spherical.

An open question is how compact nanodosimeters can be used in therapeutic radiation fields. The current detector design uses a trigger for the incoming particles. Obviously, this is not possible in a radiation field and only conditional cluster sizes can be determined. Another problem is the impact of the detector chamber on the cluster size. Interactions of the therapeutic radiation field with the detector chamber materials could create undesired ionizations that distort the cluster size distribution in a water-equivalent material. Therefore, the material of the chamber must be optimized for use in the clinic (e.g. usage of tissue-equivalent

material).

We would like to emphasize that the performance of the nanodosimeter is not yet stable.

Many open issues must be further investigated such as the stability of the detector response function, the reproducibility of the measurements, the dead time, the size of the sensitive volume and the influence of ageing of the dielectric material and of the glass cathode on the efficiency.

In conclusion, it should be emphasized that this is an initial report of preliminary results and the measurements need to be expanded to a more detailed systematic study in order to fully characterize the detector.

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Figure 1: A sketch of the experimental set-up is shown. The ceramic plate with a hole is inserted in the lid of the chamber. The chamber is filled with a low-pressure propane gas. A collimated americium-241 source emits alpha particles which ionize the gas molecules. The emitted alpha particles are registered by a surface barrier detector (SB Detector) which triggers the electronic recording of the ion signals. The hole in the ceramic plate is covered with a low-resistive glass which serves as a cathode. On the bottom of the ceramic plate is a readout electrode which is grounded. The electric field lines are shown in the relevant section of the detector. They are calculated with the COMSOL Multiphysics Modeling software.

Figure 2: A picture of the ceramic nanodosimeter detector is shown. The diameter of the visible ceramic disc is 43.9 mm and the hole diameter is 1.5 mm. The two collimators together with the scattering filter provide a well collimated beam. During measurements the part of the ceramic plate which is visible in this picture, is covered with a copper tape and connected to ground. For better visibility it was removed for this picture. The surface barrier (SB) detector triggers the acquisition window when it detects an alpha particle.

(a) Diameter of the spherical volume is 2.5 nm. The black squares represent the measured cluster size from the first experimental run.

(b) Diameter of the spherical volume is 2.5 nm. The black squares represent the measured cluster size from the second experimental run.

(c) Diameter of the spherical volume is 5 nm.

(d) Diameter of the spherical volume is 7 nm.

Figure 3: The experimentally obtained cluster size distributions (black squares) and the Bayesian reconstructed cluster size distributions (blue circles) are shown. The red triangles represent the cluster size distributions simulated with TOPAS in spheres of liquid water. The cluster size distributions calculated from the simulated Monte Carlo cluster size distributions using the binomial probability are also shown (yellow diamonds).

354 "The authors have no conflicts to disclose."