Developments in microdosimetry and nanodosimetry for space and therapeutic applications

Andrew J. Wroe
University of Wollongong
NOTE

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9 Low-Pressure Gas Nanodosimetry

9.1 Introduction

This report has demonstrated the ability of microdosimetry to provide information on a radiation field at the micron or cellular level. The next logical step is to extend this work to measuring radiation interactions on the level of DNA, as it is radiation interactions with DNA producing base lesions, single strand breaks and double strand breaks which determines biological effect. Also as electronic circuits continue to advance and in turn decrease in size, measurements on the nanometre level will possibly provide a more accurate analysis of SEU rates, allowing for the incorporation of design features to extend deployment life-times. Experimental low-pressure gas nanodosimetry provides a means for measuring radiation interactions within a nanoscopic or DNA equivalent volume and will be investigated and presented upon.

The investigators at LLUMC, in collaboration with the Weizmann Institute of Science and the Santa Cruz Institute of Particle Physics, have built and optimized two ion counting nanodosimeters (ND). The operation of this device has been described previously in Section 2.6.2. One of these devices is currently installed on the PWEST research beam-line at Loma Linda University Medical Centre. This device is equipped with a Silicon Tracking Telescope (STT) [42] which allows for the analysis of incident particle track with respect to cluster formation within the Sensitive Volume (SV). This device was utilised to obtain the nanodosimetric spectra or ionisation cluster frequency distribution for a range of incident proton energies.

Experimental nanodosimetry would also benefit from the development and validation of Monte Carlo (MC) track structure simulations, accurately reflecting the experimental radiation conditions and response of the device. Once the Monte Carlo simulation system has been developed and verified it will be possible to include more complex homogeneous and heterogeneous structures into the theoretical model. This may then provide a means for better predicting radiation effects in radiation therapy or assess radiation risks in protection applications in cases where experimental data are not available.
This section work obtained experimental data utilising the low-pressure gas nanodosimeter for a range of incident proton energies. Using the STT it was possible to complete off-line data analysis and provide experimental data for varying SV length, and various incident ion positions relative to the SV. This experimental data was compared to the output from a specially designed Monte Carlo code that has been developed by Dr Bernd Grosswendt [114] to simulate proton interactions in water and low-pressure gases. However, such a program requires accurate assessment of the radiation field present in the experimental hall. As such GEANT4.7.1p1 was utilised to simulate the transport of the initial proton beam from the accelerator through the beam modifying devices of the experimental hall up to the SV of the ND. The output files of this program were then used as input files for the simulation of the ND’s response. This study enabled an assessment of the accuracy of theoretical MC codes in simulating ionisation events on a nanometric level and identified areas of improvement that need to be addressed.

9.2 Experimental Method

Experimental data was collected for a range of incident proton energies and LET’s. The proton accelerator at LLUMC provided incident protons of energy 250 and 30.7 MeV. These were transported along the experimental setup and into the ND. In this case a degrader was used to achieve three beam energies within the ND that closely resembled the incident proton energies utilised in cell survival work, described in Section 10.4.2. The three experimental assemblies are displayed in Figure 9-1, Figure 9-4 and Figure 9-5. These achieved approximate proton energies of 250, 17 and 5 MeV within the ND SV that were verified using GEANT4 and Csl calorimetry.
Figure 9-1: Schematic of the experimental set-up for acquisition of 250 MeV proton ND data (Setup A).

In the case of the 250 MeV acquisition no degrader or additional beam modifying/monitoring devices were utilised (Setup A). The STT registered the entrance and exit positions (both X and Y) of incident ions and allowed for correlation of the incident ion track with cluster formation. In this experimental setup the four separate planes of single-sided silicon strip detectors acted in coincidence as a trigger for ND acquisition. A single broad beam acquisition was completed for 250 MeV, with the Si tracker image of the beam profile displayed in Figure 9-2. Data was collected in all cases at an average rate of 2000 events per spill (accelerator cycle of approximately 2 seconds [9]). In the 250 MeV acquisition a total of $7 \times 10^7$ particle events were collected for analysis. These events were then screened to reject pile-up events, events with more than one track or incomplete tracks, events with abnormally large energy depositions within the STT, and events with track orientation inconsistent with the beam direction. As such approximately $4 \times 10^7$ events were available for further analysis.
Using the STT and tracking information it was possible to complete off-line data cuts and analyse particles interacting with one portion of the ND SV. This is useful for comparisons with Monte Carlo simulations, and was used to generate the experimental ND spectra for incident proton tracks at three different lateral displacements from the central axis 0, 2, and 7 mm (corresponding to 0, 6 and 21 mm in tissue) at a height of 25 mm on the full SV (50 mm length total). A cross sectional profile of the ND SV and incident beam configuration (after off-line data analysis) to create the cluster size distribution (CSD) at three different distances from the SV is displayed in Figure 9-3. Further analysis of the ND performance for both a full and 7 nm long SV’s was also completed with the 250 MeV broad beam for comparison with simulated results.
For a 17 MeV proton acquisition the beam was degraded from an incident energy of 30.7 MeV with the use of a 1.54 mm thick polystyrene degrader (Figure 9-4) and is designated as Setup B. The Si tracker efficiency for protons at this energy is very poor even at reduced bias voltages (recovery time up to few seconds depending on input charge). As such the Si tracker was suitable for providing positional information but the timing characteristics precluded its use as the ND trigger. A Bicron plastic scintillator BC-408 was employed immediately upstream from the ND to provide a trigger for the data acquisition system (DAQ) and allow for reconstruction of the proton track. In this case the scintillator was wrapped in 100 μm of Al and 100 μm of black polyethylene to avoid light contamination of the signal. As in the case of the 250 MeV results, offline analysis of the measured signal allowed for the experimental ND spectra to be obtained for 0, 6 and 21 nm lateral displacements from the SV at a height of 25 mm for further validation of the simulation program.
Figure 9-4: Schematic of the experimental set-up for the acquisition of 17 MeV proton ND data (Setup B).

For the collection of 5 MeV data, the experimental setup had to be changed significantly to compensate for the lower energy protons entering the ND (Figure 9-5) and is designated as Setup C. Firstly the STT could not provide viable data on particle position (entering and exiting the NS SV) due to poor efficiency and as such the entrance module (consisting of 2 single sided Si strip detectors) was removed. As in 17 MeV data collection, the plastic scintillator provided triggering for the ND. To minimise spurious triggering on particles that were scattered and did not enter the ND a lead collimator of 1.57 mm thickness was employed immediately upstream of the scintillator with a vertical slit of 1 x 0.2 mm². This was coupled with a 0.5 mm thick polystyrene collimator within the ND assembly (in place of the STT) that also had a vertical slit of 1 x 0.2 mm². The entrance window to the ND was also changed from 0.2 mm Al to 0.1 mm G10 to allow for the effective transport of low energy protons into the ND. The polystyrene degrader at the beam pipe exit was increased in thickness to 5.8 mm to obtain an energy of approximately 5 MeV in the ND (this was verified with GEANT4 simulations and CsI measurements).
Figure 9-5: Schematic of the experimental setup used to obtain 5 MeV proton ND data (Setup C).

As experimental data was required for 3 lateral positions from the central axis (i.e. 0, 2 and 7 mm) at a height of 25 mm above the base of the SV the particle position needed to be isolated and determined for off-line analysis without the use of the front STT. To achieve this, two polystyrene screens were set up at the entrance and exit of the ND chamber. These screens had a horizontal slit measuring 1 x 50 mm² at a height of 25 mm. As such all particles crossing the ND SV would do so in a 1 mm thick horizontal band at 25 mm above the base of the SV. A single plane on the rear STT was then used to collect the X position of the particle crossing the SV. As the Y position was already known through collimation, off-line data analysis would allow for the determination of CSD with incident protons crossing the SV at a height of 25 mm and at a lateral distance of 0, 2 and 7 mm from the SV for comparison with Monte Carlo simulations.

In both the case of 17 and 5 MeV proton measurements the proton energy entering the ND SV was measured using a CsI calorimeter. This allowed for fine tuning of degrader thicknesses and checking of the experimental setup. The energy spectra produced through calorimeter measurements was compared to GEANT4 simulation results to further validate simulations of the experimental conditions.
9.3 Simulation of Experimental Beam Conditions

Monte Carlo codes provide a powerful tool to validate and improve experimental nanodosimetric systems and, once verified, could provide additional data without performing time-consuming and expensive accelerator experiments. For verification, it is important to accurately simulate the experimental conditions present whilst taking measurements with the nanodosimeter in order to obtain an accurate comparison.

For these simulations it was vital that accurate information on the beam incident on the nanodosimeter be obtained. To achieve this, the GEANT4.7.1p1 Toolkit [52] was used to simulate the research beam line at LLUMC and experimental ND set-up for the three configurations outlined in Section 9.2. The beam modifying devices and regions that were simulated within the geometry module of this program included the evacuated beam line, secondary emission module (SEM), entrance and exit windows, air gaps, STT, degraders, collimators and SV gas material. Dimensions and composition of these beam modifying devices are provided in Table 9-1. Elements making up materials utilised within the phantom geometry were defined by isotopic abundance. This provided the most accurate composition available and was obtained from an ICRU based program [35] and defined at standard temperature and pressure (except the SV gas which is given a pressure of 133.32Pa).

In addition to all materials defined in Table 9-1 the stainless steel casing of the beam pipe, SEM and ND were also constructed. It should be noted that in the case of the scintillator, it was wrapped within a layer of 0.1 mm Al and 0.1 mm cellulose, and as such the beam traversed these coverings twice (i.e. as it enters the scintillator and then as it exits). Further, all collimator aperture dimensions were constructed as described in Section 9.2.
<table>
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<tr>
<th>Modifying Device</th>
<th>Thickness (mm)</th>
<th>Material</th>
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<td>Vacuum</td>
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<td>SEM Foils</td>
<td>$1.27 \times 10^{-2}$ (5 foils)</td>
<td>Aluminium</td>
</tr>
<tr>
<td>Beam-line exit Window</td>
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<td>Titanium</td>
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<td>Polystyrene</td>
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<tr>
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<td>Bicron-B400</td>
</tr>
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<td>0.10 (2 layers)</td>
<td>Aluminium</td>
</tr>
<tr>
<td>Scintillator Poly Wrap</td>
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<td>Cellulose</td>
</tr>
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<td>Aluminium</td>
</tr>
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<td>Kapton</td>
</tr>
<tr>
<td>Silicon Tracker (250 &amp; 17 MeV)</td>
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<td>Silicon</td>
</tr>
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<td>Polystyrene</td>
</tr>
<tr>
<td>Collimator Screens (5 MeV)</td>
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<td>Polystyrene</td>
</tr>
<tr>
<td>ND Gas</td>
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<td>Propane</td>
</tr>
</tbody>
</table>

Table 9-1: Composition and thickness of beam modifying devices comprising the proton-east research beam-line at LLUMC.

As in the microdosimetry simulations completed in this thesis, the physics processes were accounted for using a modular design based on the hadron therapy example released with the GEANT4.7.1p1 toolkit. Low energy inelastic scattering, low energy ionisation and multiple scattering models were employed for the transport of protons through the geometry of the simulation, while inelastic interactions were considered using the G4preCompound model. The physics of secondary particles also needed to be considered and accounted for. In the case of alpha particles, deuterons, tritons, and other generic charged ions produced as a result of inelastic proton interactions, the corresponding low energy inelastic scattering, low energy ionisation and multiple scattering models were utilised. The predominant particles generated within the simulation would be electrons resulting from proton ionisation interactions. Electron processes accounted for included low energy ionisation, low energy Bremsstrahlung and
multiple scattering. In the event of photon generation, the physics processes included were low energy photoelectric effect, low energy Compton scattering, low energy Rayleigh scattering, and low energy pair production. Neutron interactions were also accounted for using the appropriate models. As only incident protons could be considered by the ND simulation program the transport of secondaries was largely discounted through the use of a 20 mm range cut for photons, electrons and positrons. This had the added benefit of improving simulation times. For analysis of the secondary particle spectra entering the ND, selected simulations were completed with a 10 μm range cut employed for electrons and photons.

The incident radiation beam was defined in the GEANT4 application by energy, energy spread, cross sectional area, and divergence. In the case of 250 MeV incident proton simulations the beam was considered to have a σ=40keV and a beam radius of 10 mm with no divergence [116]. In the case of 30.7 MeV incident proton simulations the beam was approximated as monoenergetic with zero divergence and a beam radius of 5 mm.

The SV assigned within the GEANT4 based application was a 1 μm thick gas volume within the ND downstream of the STT or collimators. The cross sectional area and placement of the SV was dependant on whether broad beam data or information on the energy spectra at varying lateral displacements from the SV was required. In the case of broad beam data acquisition (completed for 250 MeV only), the SV within the application was considered as a 10 cm diameter cylinder covering the cross sectional area of the ND. All protons interacting within the volume (whether depositing energy or not) had their kinetic energy and position of interaction logged allowing for the generation of both spectral and fluence distributions. Broad beam simulations were completed for 5x10^6 incident proton histories.

For simulations of the ND response for incident proton tracks at a given height and lateral displacement from the SV, three 1x1x0.001 mm^3 volumes at a height of 25 mm and lateral displacement from the central axis of 0, 2 and 7 mm were utilised. For protons interacting with these volumes, the kinetic energy was logged and a separate
proton kinetic energy distribution was created for each SV, as such each simulation output 3 separate energy spectra files. Due to the small cross sectional area of the SV’s simulation times needed to be increased to $1.2 \times 10^9$ incident histories to allow for sufficient statistics.

9.4 GEANT4 Simulation Results

The GEANT4 simulation of the beam modifying devices provided beam fluence (in the case of 250 MeV broad beam simulations) and energy spectra data that enabled an accurate assessment of the beam conditions entering the nanodosimeter.

In Figure 9-6, the energy spectrum of the incident proton beam before traversing the beam modifying devices is shown to have a mean energy of 250 MeV with $\sigma = 40$ keV, as per the experimental beam conditions at LLUMC for experimental Setup A. After traversing the beam modifying devices, the beam has lost energy and undergone range straggling, resulting in a non-symmetrical peak with a low energy tail. The most probable proton energy is 248.9 MeV with a FWHM of approximately 0.3 MeV. Unfortunately, the CsI calorimeter used in proton energy validation is not of sufficient size to collect the entire proton energy for a 250 MeV beam and as such cannot be used to verify the simulated energy spectra within the ND.

The GEANT4-based application provided not only accurate peak information but also information regarding low energy protons. These low energy protons are present below the peak energy and range down to energies of only 2MeV. Whilst not in any great abundance, these low energy protons have an elevated LET that could lead to increased cluster formation within the SV of the nanodosimeter. In order to accurately assess the impact of low energy protons, two files were output from this program. The first file gave the peak energy spectra between 247 and 249.4 MeV while the second gave the low energy spectra of all proton energies below 247 MeV. The nanodosimetric cluster frequency distributions from both underwent a weighted summation based upon the relative number of histories in each input file to supply the total theoretical cluster distribution.
Figure 9-6: Simulated energy distributions of the LLUMC 250 MeV proton beam before and after proceeding through the beam modifying devices (Setup A). Distributions were normalised to peak frequency.

As per the experimental beam conditions, the incident beam prior to entering the beam modifying devices had a uniform profile and a radius of 1.0cm (Figure 9-7). Once passing through the beam modifying devices including SEM foils, air gap, nanodosimeter entrance window and Si strip detectors, the beam has spread significantly appearing Gaussian in shape and extends out to a radius of 1.0cm at FWHM. This fluence distribution was used as the input for 250 MeV broad beam simulations of nanodosimeter response.
Figure 9-7: Simulated radial distributions of the LLUMC 250 MeV proton beam before and after proceeding through the beam modifying devices (Setup A). Distributions normalised to central bin frequency.

Using the geometry of the experimental setup used in the collection of ND data for 17 MeV protons (experimental Setup B) the energy spectra of the proton field entering the ND SV was simulated. This is compared with the experimentally measured value using a CsI calorimeter in Figure 9-8. The agreement between the experimental and simulated peak positions is excellent with values of 16.8 and 16.875 MeV respectively. The simulated spectra FWHM is not as broad as in the experimental case and this is a direct result of an assumption that the incident radiation field was monoenergetic. Future simulations can consider this, however, it must first be determined accurately within the accelerator transport system. Broadening of the experimental spectra can also be attributed to electronic noise in the experimental measurement system that was not considered in the simulated case.
Figure 9-8: Comparison of simulated and experimentally measured energy distributions for incident protons entering the ND using experimental setup B (i.e. to achieve approximately 17 MeV protons within the ND).

The energy spectrum of the incident proton radiation field was also simulated using GEANT4 for the case of experimental setup C (to achieve 5 MeV protons within the ND). The simulated results are plotted against experimentally measured energy spectra using a CsI calorimeter and displayed in Figure 9-9. Agreement is excellent between the simulated and experimental cases with a 20 keV difference in mean peak position between the two spectra. Again the experimental case exhibits a larger FWHM which is attributed to spread in the initial beam energy and also in electronic noise of the calorimetry system.
Figure 9-9: Comparison of simulated and experimentally measured energy distributions for incident protons entering the ND using experimental Setup C (i.e. to achieve approximately 5 MeV protons within the ND).

The simulated energy spectra (i.e. devoid of any experimental system noise and considered the ideal case) was used as input into a separate Monte Carlo program used to simulate the response of the ND. The use of such spectra will possibly allow for a more accurate simulated ND response as it will consider the incident radiation field.

9.5 ND Simulation Program

As ionisations within a nanoscopic volume were to be measured and cluster size determined, it was imperative that it be possible to simulate electrons down to the ionisation potential of the gas or 10 eV. Unfortunately GEANT4.7.1p1 can only transport electrons to an energy limit of 250 eV making it unsuitable for simulations of ND performance. In order to produce accurate simulations of the experimental conditions the GEANT4.7.1p1 based application provides the energy spectra and fluence (broad beam only) distribution of protons (both primary and secondary) incident into the ND SV as two separate output files. These output files were used as initial history input for a
special Monte Carlo code that has been developed by Dr. Bernd Grosswendt at Physikalisch-Technische Bundesanstalt (PTB), Braunschweig, Germany to simulate proton interactions in water and low-pressure gases [114]. A detailed description of this program can be found in the appendix of [37].

Figure 9-10: Correlation between measured ion drift time in Propane and vertical track co-ordinate [115].

The PTB Monte Carlo code was written in FORTRAN and utilises a compilation of experimental ionisation cross sections of protons and experimental electron interaction cross sections for elastic scattering, excitation and ionisation to transport high-energy protons and secondary electrons with energies down to 10 eV (the ionisation potential) in propane. The geometry utilised within this program, consisted of a wall-less homogeneous 1 Torr propane gas volume of 5x5x3 cm³ embedded with the sensitive volume in which the position and number of ions was registered. The positions of the ions on a proton track segment in the SV were transformed into an ion-signal pulse train using a calculated three-dimensional efficiency map of the SV [37, 38] and the experimentally measured ion space–drift time relationship (Figure 9-10). Noise of the ND ion channel was accounted for by introducing random pulses corresponding to the frequency of those measured (i.e. 5 Hz). Simulations were completed for $10^7$ incident proton histories to ensure adequate statistics.
9.6 ND Simulation Results & Discussion

Simulation of the response of the ND is presented in this section with direct comparison to experimentally measured ND response.

9.6.1 250 MeV Broad Beam

Simulations of the ND response to a 250 MeV broad beam utilised both the energy spectra and fluence distribution files generated by the GEANT4 based application as input for the ND simulation program. GEANT4 provided information regarding the entire proton energy spectrum entering the nanodosimeter from an incident 250 MeV proton beam, including recoil protons that are produced through nuclear scattering with the beam modifying devices upstream of the ND. The effect of these particles on ND spectra was determined by running separate simulations for the peak and lower energy spectra and summing these based on the relevant number of histories as provided by GEANT4 (Figure 9-11). It was assumed in these simulations that the fluence distribution (Figure 9-7) of particles making up the peak and lower energy spectra was identical.

![Cluster size distribution comparison](image)

**Figure 9-11:** Cluster size distribution comparisons of peak, lower and summed simulation results normalised to the total number of events including zero events. Error bars contained within data points.
As could be expected for the same number of histories, the lower energy protons produce a higher probability of cluster formation (and hence ionisation or damage) within the DNA equivalent volume, which is indicative of their higher LET. However, in actual fact these lower energy protons comprised less than 0.5% of the total number of protons entering the nanodosimeter volume. When this weighting was applied and both results summed the effect from the lower energy protons is seen as negligible (Figure 9-11).

Figure 9-12a) illustrates a comparison between experimental and Monte Carlo cluster size distributions (transport of all low energy protons considered) including zero-events (proton events without any ion detection in the SV). Figure 9-12b) displays a comparison between experimental and Monte Carlo cluster size distributions excluding zero-events. The experimental cluster size distribution including zero events exhibits good agreement with the simulated results up to a cluster size of 8. In this region the simulation tends to over estimate the response of the ND with as much as a 30% increase over the experimental values. At cluster sizes greater than 8, the simulation under-estimates the response of the ND dramatically with as high as a factor of five variation in the frequency of cluster formation. The over-estimation of small cluster formation (less than 8 ions) and under estimation of large cluster formation by the Monte Carlo program is largely negated when using the mean cluster size (MCS) as an analysis parameter. In this case the experimental MCS is $5.68 \times 10^{-3}$ compared to the theoretical MCS of $5.53 \times 10^{-3}$, which is a variation of approximately 2.5%.

For the cluster size distributions excluding zero events (Figure 9-12b) a similar trend is observed. For small cluster formations the Monte Carlo results exhibit an over-estimation of cluster formation (with the exception of a cluster size of 2), however such discrepancies are small and the simulation program exhibits good agreement with experimental values in this region. For large cluster formation (7 ions or larger) the experimental frequencies become progressively larger than the simulated frequencies as cluster size increases.
Figure 9-12: Cluster size distribution comparisons for theoretical and experimental results. a) Distribution normalised to the total number of events, including zero events; b) Distribution normalised to the total number of events with at least one ion (cluster size ≥1). Error bars are contained within data points.
The higher frequency of large clusters under experimental conditions could indicate that particles generating additional ionisation events are entering the ND gas volume that is not accounted for in the simulation. The simulation only accounts for protons entering the gas volume and as such the source of the additional clusters could be secondary electrons produced in the upstream silicon strip detectors as well as neutron contamination of the beam. To assess this, the spectrum of secondary electrons entering the ND was simulated using the GEANT4 based application.

![Energy spectra of electrons entering the nanodosimeter as simulated using the GEANT4 based application created for this study. The spectra was normalised to the total number of events.](image)

**Figure 9-13:** Energy spectra of electrons entering the nanodosimeter as simulated using the GEANT4 based application created for this study. The spectra was normalised to the total number of events.

It is clear from Figure 9-13 that electrons of a range of energies produced by the beam modifying devices are entering the nanodosimeter. Electrons ranging in energy from only a few hundred eV, which were most abundant, to just over 600 keV would go on to contribute to cluster formation within the SV. Low energy electrons could contribute to large cluster formation as they have the potential to stop within the SV. Indeed, there was approximately one electron for every 20 protons entering the nanodosimeter chamber. These secondary electrons could be the cause of the variation between the
experimental and simulated results. Increasing discrepancy of the conditional cluster size distributions for >8 ions may be due to stopping electrons or neutron contamination, since these would preferentially contribute large clusters. This effect could also be produced by a rare ion multiplication mechanism in the ion acceleration channel below the ND aperture as suggested by [37]. Further investigation of this is required and ideally it would be useful to complete simulations of ALL particles entering the ND under experimental conditions for comparison with experimental results.

9.6.2 Incident Track Validation

To further validate the combined Monte Carlo simulation system used to theoretically determine the response of the ND, experimental data was obtained for three separate proton energies 250, 17 and 5 MeV. Using the STT and off-line data analysis it was possible to isolate the experimental response of the ND to incident protons crossing at a height of 25 mm from the base aperture and at three different lateral displacements from the SV, 0, 2 and 7 mm in gas which corresponds to 0, 6 and 21 nm in tissue. Using the GEANT4 based application three separate energy distribution files were generated using the experimental conditions present during data collection (Section 9.4). These were used as input into the ND simulation program with the incident energy of the beam governed by the distributions generated by GEANT4 and the position of the beam localised to a co-ordinate corresponding to a height of 25 mm and a distance from the SV of 0, 2 or 7 mm. Separate simulations of $10^7$ particles were run for each co-ordinate and the comparative results displayed in Figure 9-14, Figure 9-15 and Figure 9-16.
Figure 9-14: Cluster size distribution for ~250 MeV protons at a distance of 0, 6 and 21 nm from the SV generated experimentally and theoretically. Appropriate error bars are displayed for experimentally measured values.

The results generated for the 250 MeV beam are in good agreement across a range of generated cluster sizes. Some discrepancy is observed between the simulated and experimental cases for larger cluster sizes (>8 ions) which has been addressed previously in broad beam simulations. It is surmised that this discrepancy results from secondary particles entering the ND which are not considered in the simulation system, or possibly from a rare ion multiplication mechanism in the ion acceleration channel below the ND aperture as suggested by [37]. It is important to note that this discrepancy is most prevalent for 250 MeV at 0 mm lateral displacement from the SV yet is not observed in the 17 and 5 MeV cases (Figure 9-15 and Figure 9-16). As the neutron spectra present for experimental measurements is significantly reduced and almost non-existent for both of these energies (as the incident proton energy is only 30.7 MeV) it could be surmised that the increase in the frequency of large clusters for 250 MeV is a result of neutrons present in the radiation field that are not considered by the simulation program. This
supports the development of code that will account for these particles in cluster formation. Such results may also be useful in determining the effect of secondary neutrons in proton therapy treatment, especially when linked with a radiobiological model.

Figure 9-15: Cluster size distribution for ~17 MeV protons at a distance of 0, 6 and 21 nm from the SV generated experimentally and theoretically. Appropriate error bars are displayed for experimentally measured values.

For 17 and 5 MeV the comparative results are in good agreement with no significant deviations in the trends expressed by the experimental or theoretical results. It is apparent from Figure 9-15 and Figure 9-16 that at a lateral displacement of 21 nm (or 7 mm) from the SV, the experimental results do not exhibit a smooth trend. It is believed that this is a direct result of limited statistics in this region, as due to beam time constraints the number of histories collected for 17 and 5 MeV was only approximately 10% of those collected in 250 MeV experiments. Future work will be completed to
improve the number of collected histories for these energies and expand the results to other particles and proton energies.

![Cluster Size Distribution Graph](image)

**Figure 9-16**: Cluster size distribution for ~5 MeV protons at a distance of 0, 6 and 21 nm from the SV generated experimentally and theoretically. Appropriate error bars are displayed for experimentally measured values.

In the case of 5 MeV protons, the simulations do reflect the experimental trends well, however in both the case of the 0 and 6 nm lateral displacements from the SV the theoretical results over-estimate the response of the ND. It is possible that this is a reflection of the discrepancies in the FWHM of the experimental (measured using a CsI calorimeter) and theoretical beam profile generated by GEANT4. Further work should be completed to incorporate accurate initial beam energy distributions and fluence maps into the GEANT4 application to obtain a more accurate spectrum of particles entering the ND. Such improvements should result in a more accurate theoretical response of the ND, especially at low energies where the beam has been degraded significantly from its incident energy.
Figure 9-17: Mean cluster size as a function of lateral displacement from the SV at a height of 25 mm for 250, 17 and 5 MeV protons.

Figure 9-17 displays the MCS as a function of lateral displacement from the SV for the three proton energies tested. The results returned are interesting and provide information on the range of secondary electrons generated by the different incident radiations. Clearly the MCS increases as the incident particle LET and hence as the ionisation density increases. Further, it would be expected that the MCS also varies depending on particle type and associated track structure at the nanometre level which has been observed in previous work [37, 38]. At a height of 25 mm and with no lateral displacement there is a factor of 9 difference in MCS between 250 and 17 MeV protons while this increases dramatically to a factor of 27 difference when comparing 250 and 5 MeV protons. However, as the lateral displacement increases the difference in MCS between 250 MeV, 17 and 5 MeV protons decreases. Such that at a lateral displacement of 21 nm there is a factor of 4 difference in MCS between 250 and 17 MeV and a factor of 10 difference when comparing 250 and 5 MeV protons. As the lateral displacement
has increased from 0 to 21 nm the difference in MCS from 250 to 17 and 250 to 5 MeV protons has decreased by a factor of approximately 2. This illustrates that while 250 MeV protons may be sparsely ionising, electrons produced have potentially longer ranges than for lower energy protons. Long range delta rays can interact with DNA at distance from the incident particle track increasing biological damage. This data has further displayed how nanodosimetry provides information on particle track structure that is dependant on particle type and energy. Variations in either produce a measurable change in nanodosimeter response as observed in data presented above and in [40]. Such changes can in turn be correlated with biological effect (Section 9.8.2) and further supports the use of such quantities in treatment planning to better ascertain radiobiological effect from therapeutic radiation fields.

9.6.3 Effect of Electron Transport

The effect of secondary and Auger electron generation and transport in the gas volume was also investigated using a broad beam of 250 MeV protons and the results are displayed in Figure 9-18. It is clear that secondary electron interactions within the SV contribute significantly to cluster sizes larger than one ion, with only small cluster sizes deriving from direct proton ionisation within the SV. This is to be expected as a direct result of a high-energy proton's low LET producing a low-density ionisation track. Secondary electrons that are produced within the gas and traverse the SV can produce further ionisations within the DNA equivalent volume. It is the ionisations produced by these secondary electrons that create most of the clusters larger than 1-2 ions within the SV. Assuming that the ND SV simulates DNA, this means that secondary electrons are significantly enhancing the biological damage produced by the primary particles.

The effect of Auger electrons on cluster size was also studied by including or excluding these electrons from the simulation (Figure 9-18). It is clear that Auger electrons produced within the gas can cause further ionisations within the SV increasing the probability of larger clusters. However, this effect is quantitatively small when compared with the effect of all secondary electrons.
9.6.4 Dependence of CSD on SV Length

In all previous cases a full length (50 mm in gas) SV has been utilised in comparisons between experimental and simulated nanodosimetric CSD. However, it is also important to ascertain the accuracy of the simulation program for shorter SV’s. To determine this, offline analysis of experimental data using appropriate cuts on ion drift time was conducted to achieve experimental data for an equivalent SV length of 7 nm (in tissue) irradiated with a 250 MeV broad proton beam (Setup A). These were then compared with simulated data for an equivalent 7nm SV within the nanodosimeter. As in previous cases the GEANT4 based application provided the energy and fluence spectra for a 250 MeV broad beam to the program that determines CSD within the nanodosimeter.
Figure 9-19: Cluster size distribution comparisons for theoretical and experimental results utilising both full and 7nm SV lengths. The distributions are normalised to the total number of events including zero events.

The simulated and measured CSD’s for the 7 nm SV show good agreement for smaller cluster sizes and is similar to the results obtained for the full SV case. A discrepancy is observed between the theoretical and experimental results for large cluster sizes with the simulation under-estimating the response of the ND. It is important to note that both the simulated and measured frequency of clusters formed within the 7 nm SV is of an order of magnitude smaller than that for the full SV. For the simulated results this discrepancy between the two SV sizes increases as cluster size increases. The first observation is explained by the difference in the SV size, as the geometrical cross section of the primary beam and SV is about 10-times smaller for the 7 nm SV than for the full SV. The second observation can be explained by the fact that many of the larger clusters may not fit into a 7 nm volume and are therefore registered as smaller clusters with part of the cluster lying outside the SV.
The final observation from these results concerns the discrepancy between simulated and measured CSD for larger clusters. For the 7nm SV one observes that the measured cluster frequency departs from the simulated one at a cluster size of about 4-5 and then decreases with a similar slope as the measured CSD for the full SV (Figure 9-19). This result favours the already mentioned ion multiplication mechanism below the aperture [37], which would be independent of the selected SV size, as an explanation for the additional large clusters observed experimentally.

9.7 Conclusion

This work has investigated the effectiveness of the GEANT4 toolkit in obtaining incident beam data to achieve a simulated input for an independent ND simulation code. The GEANT4 based application created for this work provides a means for simulating the beam modifying devices that the radiation field must pass through before entering the nanodosimeter. The results obtained were compared where possible to Csl calorimeter measurements with good agreement in mean peak position observed. Further improvements including a more accurate estimation of the cross sectional area, divergence and energy spread of the delivered beam could be incorporated into future work to provide a more accurate assessment of the radiation field present during experimental measurements.

The output from GEANT4 was then processed by the PTB simulation code to compute theoretical nanodosimetric cluster size distributions. This two-stage simulation system allows for a more accurate assessment of the radiation field entering the nanodosimeter and provided better agreement between experimental and simulated cluster size distributions. The simulated response of the ND was compared to experimentally derived results over a range of energies and beam configurations.

Broad beam 250 MeV simulations were completed with the GEANT4 generated energy spectra and fluence distribution input into the ND simulation. In this case the GEANT4 based application provided the entire energy spectra of protons entering the SV including both the peak low energy recoil protons. Whilst the low energy protons make up less than 0.5% of all protons entering the SV, separate simulations of both the peak
and low energy proton spectra were conducted to ascertain their importance, or lack of, to CSD. Indeed the low number of recoil protons entering the nanodosimeter makes their contribution to CSD insignificant. Some discrepancy was observed in comparison between the simulated and experimental CSD especially for larger clusters where it appears that the simulation program under-estimates the response of the ND. It is believed this is caused by secondary electrons and neutrons produced in the up-stream beam modifying devices of the system. The ND simulation program in its present form is limited in that it can only account for one type of incident radiation, protons in this case. However, after passing through beam modification devices the radiation field will not only comprise of protons, but low-energy secondary electrons and also neutrons, both of which are likely to contribute to the additional clusters within the nanodosimeter observed experimentally. In order to improve the accuracy of the nanodosimeter simulation program, particles such as secondary electrons and neutrons produced in upstream devices and entering the gas volume also need to be accounted for. It is also possible that this discrepancy could also be caused by a rare ion multiplication mechanism in the ion acceleration channel below the ND aperture as suggested by [37].

Pencil beam simulations were also completed for 250, 17 and 5 MeV protons at a height of 25 mm on the SV and lateral displacements of 0, 2 and 7 mm in gas (or 0, 6, and 21 nm in tissue). These were compared with experimental data that was obtained through off-line analysis using the STT. The comparison between experimental and theoretically derived CSD’s was good with discrepancies at larger cluster sizes observed as a result of secondary particles not accounted for in the simulation and limited statistical sampling. The trends of the experimental response were well reflected further validating the Monte Carlo simulation system employed in this work and identifying areas of future development. These measurements indicated the ability of the experimental and theoretical systems in measuring the change in track structure (nanometric radiation properties) of radiations of the same type but differing LET.

The importance of secondary electrons generated inside the nanodosimeter to cluster size was highlighted through simulations of the response of the ND to a broad beam of 250 MeV protons considering all electrons, discounting Auger electron formation and
discounting electron transport altogether. It was observed that secondary electrons are the main contributors to cluster sizes larger than two ions for 250 MeV proton irradiation of a nanometric volume, while Auger electrons make only a small contribution to cluster frequency.

Finally, the response of the ND to varying SV length was simulated for a 250MeV broad beam and compared with experimental data that was obtained using appropriate cuts on ion drift time for a 7 nm SV. The results indicated good agreement between the experimental and simulated cases for small cluster sizes. However, for both the 7 nm and full SV the simulation program tended to underestimate the response of the ND for large cluster sizes. The frequency of cluster formation for the 7 nm SV was approximately an order of magnitude lower than for the full SV, and this discrepancy increased with increasing cluster size. This later is most likely the direct result of larger clusters being unable to be contained within the smaller SV.

These results have presented both theoretical and experimental nanodosimetry data for a range of proton energies. The Monte Carlo system employed has been validated through these comparisons and areas of improvement have been identified for future work. The current ND system has demonstrated that it is useful in obtaining nanodosimetric data for laboratory conditions and supports the program we have implemented for the investigation of nanodosimetry and its importance to radiation therapy and radiation protection. Information on the nanometric cluster size distribution (or track structure) of an incident particle may provide a more accurate determination of radiation effects of mixed radiation fields, as the track structure of a given charged particle at a given energy is unique. Experimental measurements and theoretical simulations have shown that such measurements are possible using low-pressure gas nanodosimetry and associated Monte Carlo simulation systems. This may then be linked to an accurate prediction of RBE through the development of a biological model. Further work on detector development including improvements to portability, collection times, and ability for in-phantom measurements will also increase the application of nanodosimetry.
9.8 Future Work

Nanodosimetry is certainly an area in radiation metrology that will increase in its application for both radiation therapy and radiation protection. This work has benchmarked the performance of a low-pressure gas ion-counting nanodosimeter in proton radiation fields and compared this to a current Monte Carlo simulation system. There are three main areas of development that will be undertaken as a continuation of this work:

- Monte Carlo Simulations
- Radiobiological Modelling
- Detector Development

9.8.1 Monte Carlo Simulations

This work employed a two-stage Monte Carlo simulation system to provide the most accurate simulation of the ND response using current technologies. The first stage utilised a GEANT4 based application to simulate the primary radiation transport through beam modifying/monitoring devices and provide an accurate assessment of the radiation field entering the ND. However, GEANT4.7.1p1 can only transport electrons down to an energy of 250 eV which is insufficient for ND applications. In this field of endeavour, the electrons need to be transported down to the ionisation potential of the gas or approximately 10 eV in this case. To achieve this, a Monte Carlo simulation system developed at PTB incorporated the single particle (proton in this case) energy and fluence spectra from GEANT4 in simulating the ND response. The results obtained with such a system were satisfactory, however deficiencies were identified in the simulation system that need to be addressed in future work including:

- Assumptions in incident beam energy, profile and direction. In this case the incident beam was assumed to be monoenergetic, circular in profile and travelling normally down an evacuated beam pipe.

- Secondary particles of a different type to the primary could not be considered in the second stage of the simulation. As such neutrons and electrons were not considered in contributing to cluster formation in the experimental case.
- Particles entering the second stage of the simulation were considered to be entering normally with no angular divergence.

- Broad beam simulations simplified the particle fluence entering the ND as a radial profile, and discounted inhomogenaities in particle fluence.

- The second stage of the system can only consider ND cluster formation in a uniform propane or water volume and cannot be expanded in its current state to simulate CSD's in other structures such as tissues for radiation therapy or silicon for SEU analysis.

These deficiencies have not contributed to significant errors in the current work which is evident through the good agreement with experimentally derived data. However, it provides a clear area of future development. Many of these issues can be addressed using a single Monte Carlo simulation system such as GEANT4 to simulate both the experimental setup and ND response. Such comparisons would validate GEANT4 and allow for an expansion of ND simulations to other geometries. Unfortunately the current status of GEANT4 precludes its use simulating the ND as electron transport does not extend down to 10 eV. Significant efforts are currently being invested into the development of numerical simulation codes modelling particle track structure on the nanometre scale including the GEANT4 DNA project [47]. The ion-counting nanodosimeter and current simulation system can be used in validating improvements made to GEANT4 low energy electron transport models. Further, once validated it may be possible to utilise GEANT4 in modelling the ND as a single stand-alone application.
9.8.2 Radiobiological Modelling

Nanodosimetry provides a means for determining experimentally (or theoretically through the use of Monte Carlo modelling) the number of ionisations within a DNA equivalent volume. To facilitate a useful analysis of the biological effectiveness of radiation fields, this output needs to be linked with a biological model. The endpoints for such a model may vary, but the quantity of most relevance to radiation therapy is colonogenic cell survival.

Radiation can interact with DNA and cause damage in a number of ways including single strand breaks (SSB), double strand breaks (DSB), modified or lost bases etc [62, 117]. Current radiobiological evidence points to the fact that DSB's are the most significant type of lesion in causing cell death [118]. A radiobiological model that correlates cluster frequency within a DNA volume to biological effect will hypothesize that the colonogenic cell survival is dependant on the difference in reparability of DSB's generated from radiations of differing LET.

DSB's can be repaired along two separate pathways, homologous and nonhomologous end-joining. In both cases nucleotides degrade the ends of the DNA and prepare it for repair post DSB formation. In homologous end-joining the DNA combines with a homologous (being equal in DNA sequence) undamaged counterpart using it as a template for repair. This form of repair is precise, however is less common and typically only occurs during S-phase in the cell cycle [119]. Nonhomologous end-joining does not require a non-damaged template but proceeds by simply rejoining the broken DNA strands. This is a fast and simple process that operates throughout the cell cycle. However, there is no guarantee that the DNA returns to its existing state and multiple DSB's in close proximity may result in misrejoining of the DNA strand. Despite this fact nonhomologous end-joining is the predominant DSB repair mechanism in human cells.
Figure 9-20: Schematic of the two pathways available for DSB repair in mammalian cells [119].

Generally, DSB’s formed through low-LET radiation interaction with DNA are repaired correctly, particularly for lower doses or smaller numbers of DSB’s (termed simple DSB’s). As the dose delivered to the DNA or the LET of the incident radiation increases there may be increased levels of misrejoining in nonhomologous end-joining repair resulting in cell death or mutation. The fact that radiosensitivity is stable throughout the cell cycle indicates that repair by homologous end-joining is limited in repairing DSB’s induced by high-LET radiation or high doses of low-LET radiation (termed complex DSB’s). Such factors need to be considered in biological modelling.
Figure 9-21: Example of a survival curve for high and low LET radiations. Note the differences in response produced by individual simple, multiple simple and complex DSB’s.

Cell survival curves are generally described by a relationship between the surviving fraction of cells and the dose applied (Figure 9-21). The exponential response of the surviving fraction as a function dose is well explained by a Poisson model. The genome consists of a large number of independent DNA segments and only a small fraction of these will be affected by DSB’s that lead to a lethal event. If the lethality of DSB’s does not depend on the presence of other DSB’s in the cell, a linear survival curve is the result when plotted in a semi-logarithmic graph. This is in fact the case for a typical high-LET cell survival curve. Survival curves generated by low-LET radiations show characteristic nonlinearities, the most universal one being a downward curvature of the cell survival curve with increasing dose. This can be explained by a linear-quadratic polynomial, where the linear part corresponds to the irreparable DNA damage and the quadratic part to damage that, in principle, can be repaired but is increasingly less likely to be repaired with increasing numbers of DSB’s present per cell.
The model described here and that will be developed in future work uses experimental or Monte Carlo simulated data describing the frequency of event sizes in nanodosimetric volumes representing a segment of DNA as the basis to predict cell survival. The nanodosimetric data is used to predict the relative portion of high-LET type or complex DSB’s and low-LET type or simple DSB’s. Measured cell survival responses to a low-LET type radiation (e.g., Co-60 gamma rays) and to a high-LET type radiation (e.g., alpha particles) will provide the basis for the model. Combining these responses with the measured changes in the ND event size distribution, it is possible to predict the cell survival response to any monoenergetic or mixed radiation field for which ND data is available.

This model [120] assumes that the dose can be divided into two fractions \( q_1 \) and \( q_2 \), where \( q_1 \) is the fraction of dose deposited in ion cluster events that lead to low-LET type DSB’s and \( q_2 \) is the fraction of dose deposited in larger ion cluster events typically generating high-LET type DSB’s. These properties are determined from the CSD as the ratio of frequencies over a certain range of cluster sizes corresponding to simple and complex DSB’s respectively. It is hypothesised that cluster sizes of 2-5 produce low-LET type DSB’s, while cluster sizes larger than 5 generating high-LET type DSB’s. Note that \( q_1 \) and \( q_2 \) do not necessarily add up to 1 because a portion of dose is also deposited in single-ion events that do not lead to DSB’s. According to this model, the surviving fraction from a delivered dose \( D \) is given by the relationship as described in Equation 9-1.

\[
SF(D) = \exp\left( -\alpha_1(q_1D) - \beta(q_1D)^2 - \alpha_2(q_2D) \right)
\]

**Equation 9-1:** Model for deriving biological response from measured ND response. \( \alpha_1 \) and \( \beta \) are simple DSB parameters produced by the low-LET radiation component, while \( \alpha_2 \) is a complex DSB parameter produced by the high-LET radiation component.

The parameters \( \alpha_1 \), \( \beta \) and \( \alpha_2 \) are cell line dependant parameters that are determined through initial testing of the chosen cell line with a low-LET (e.g., Co-60 gamma rays) and high-LET (e.g., alpha particles) reference radiation. These parameters are established through initial benchmark testing of the cell line and remain unchanged.
regardless of the beam conditions. From a measured (or simulated) CSD, beam quality factors \( q_1 \) and \( q_2 \) are derived that are dependant on particle mix and energy spectra but are considered to be independent of cell type.

Given proper benchmarking with a suitable low and high-LET reference radiation it is possible to predict in theory the colonogenic cell survival for any mammalian cell line using nanodosimetry. The key to successful modelling in this case will be a suitable radiobiological protocol which will allow for suitably accurate reference radiation experiments to be completed. To this end a radiobiological protocol has been developed and is tested in Section 10.

**9.8.3 Detector Development**

This investigation and previous studies [37-39, 116] have shown that a low-pressure gas nanodosimeter is capable of measuring ionisation clusters on a DNA equivalent volume. However, such a device has its limitations, the most prominent being its need for a dedicated beam-line, its lack of portability and slow collection times. If the realm of nanodosimetry is to be investigated further an improved nanodosimeter is required that will allow for deployments on space and aircraft, installation in radiation protection applications such as nuclear and military facilities and utilisation in radiation therapy and radiobiology. For this to take place the basic concept of the apparatus may need to be revisited.

Currently nanodosimetry is based on a low pressure gas instrument that measures the number of ions (cluster of ionisations) produced by a track of charged particles in a gas volume equivalent to the nanometric volume of a DNA segment. This was achieved using a low pressure (1 Torr) tissue equivalent gas (Propane) sensitive volume (SV) of millimetre size which is similar in mass to a DNA segment. The geometry of the gas SV is determined by configuration of the electric field which extracts the ions through a small aperture. A silicon tracking telescope allows for the position and track of incoming particles to be registered and correlated with cluster formation within the SV. The operational concept of such a device means that it is suited as a basic research device rather than for active deployment.
There are two developmental tracks which can be undertaken in order to further develop nanodosimetry. The first would involve keeping the gas concept and making it more portable, efficient and easier to use. The second would involve moving in a new direction and using current solid-state technologies in order to create nanometre sized sensitive volumes. Parallels can hence be drawn to microdosimetry and the development of tissue equivalent proportional counters (TEPC’s) and solid-state microdosimeters to fulfil the criteria of collecting the energy deposited by ionising radiation in a micrometre volume.

Further development of the electronics, tracking and acquisition system of the current ion counting device can be considered. However, problems still remain that make such a device unsuitable for tasks other than research including:

- The materials surrounding the SV, including the housing, entrance window, exit windows and silicon tracking system are not TE. As such attenuation of the radiation field and the secondaries produced by such interaction will affect results.

- The differential pumping system is by nature complicated and large in size.

- The gas system does not measure interactions on a truly nanometre volume, but rather averages effects across a millimetre sized gas volume.

- The ND and STT is only suitable in a uni-directional radiation field.

Solid-state nanodosimeters of truly nanometre SV size should be investigated and developed in order to further this field of research. Attempts to develop solid-state radiation detectors sensitive to the track structure of charged particles was recently undertaken using the response of LiF Thermo-Luminescent Detectors (TLD-100) and based on recombination of electron hole pairs in spatially correlated trapping luminescent centres of LiF detectors [121]. It was observed that the shape of the glow peak produced by the TLD depends on the track structure. However, interpretation of this data is complicated and is unable to be applied in real time nanodosimetry.
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<th>Detector Performance Parameters</th>
<th>Low-Pressure Gas Nanodosimeter</th>
<th>Solid State Nanodosimeter</th>
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</thead>
<tbody>
<tr>
<td>Efficiency of Data Collection</td>
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<td>High</td>
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<tr>
<td>Efficiency of Ion Registration</td>
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<tr>
<td>Acquisition time for data points</td>
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<td>Low (10-20 minutes)</td>
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<tr>
<td>Ability to measure neutrons</td>
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<tr>
<td>In-vivo measurement</td>
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<td>High</td>
</tr>
<tr>
<td>Susceptibility to pile up</td>
<td>High (long collection time in gas)</td>
<td>Low (fast light emission and detection)</td>
</tr>
</tbody>
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**Other Parameters**

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<th>Low-Pressure Gas Nanodosimeter</th>
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<td>System Cost</td>
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<td>Portability</td>
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<td>System Complexity</td>
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<tr>
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<td>Tissue Equivalence</td>
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</tr>
</tbody>
</table>

Table 9-2: Comparative advantages and disadvantages of current low-pressure gas nanodosimetry and proposed solid state analogue and digital nanodosimetry.

A more effective method for real time nanodosimetry utilising nanotechnology and quantum dots (QD's) is currently being explored by the CMRP under Professor Anatoly Rosenfeld. In contrast to gas nanodosimetry such a device would consider the track of a charged particle in a TE organic material. The subsequent detection of the cluster formation on this nanoscopic level would provide information on track structure with a specific signature of the 8-electron radial density distribution for a given induced radiation field. There are two methods which can be employed for solid state nanodosimetry utilising this technique, digital nanodosimetry (DND) and analogue nanodosimetry (AND). This mode of nanodosimetry has the potential for significant improvements over current technology which is outlined in Table 9-2. The development of such detectors would be useful across a range of therapeutic and radiation protection applications, however adequate testing and development needs to be conducted.