Monte Carlo Analysis and Physics Characterization of a Novel Nanoparticle Detector for Medical and Micro-dosimetry Applications

by

Matthew D. Belley

Graduate Program in Medical Physics
Duke University

Date: __________________________

Approved:

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Terry T. Yoshizumi, Supervisor

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Mark W. Dewhirst, Chair

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Haijun Song

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Junzo P. Chino

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate Program in Medical Physics in the Graduate School of Duke University 2015
Abstract

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Abstract

The outcomes for both (i) radiation therapy and (ii) preclinical small animal radio-biology studies are dependent on the delivery of a known quantity of radiation to a specific and intentional location. Adverse effects can result from these procedures if the dose to the target is too high or low, and can also result from an incorrect spatial distribution in which nearby normal healthy tissue can be undesirably damaged by poor radiation delivery techniques. Thus, in mice and humans alike, the spatial dose distributions from radiation sources should be well characterized in terms of the absolute dose quantity, and with pin-point accuracy. When dealing with the steep spatial dose gradients consequential to either (i) high dose rate (HDR) brachytherapy or (ii) within the small organs and tissue inhomogeneities of mice, obtaining accurate and highly precise dose results can be very challenging, considering commercially available radiation detection tools, such as ion chambers, are often too large for in-vivo use.

In this dissertation two tools are developed and applied for both clinical and preclinical radiation measurement. The first tool is a novel radiation detector for acquiring physical measurements, fabricated from an inorganic nano-crystalline scintillator that has been fixed on an optical fiber terminus. This dosimeter allows for the measurement of point doses to sub-millimeter resolution, and has the ability to be placed in-vivo in humans and small animals. Real-time data is displayed to the user to provide instant quality assurance and dose-rate information. The second tool
utilizes an open source Monte Carlo particle transport code, and was applied for small animal dosimetry studies to calculate organ doses and recommend new techniques of dose prescription in mice, as well as to characterize dose to the murine bone marrow compartment with micron-scale resolution.

Hardware design changes were implemented to reduce the overall fiber diameter to $< 0.9\ mm$ for the nano-crystalline scintillator based fiber optic detector (NanoFOD) system. Lower limits of device sensitivity were found to be approximately 0.05 cGy/s. Herein, this detector was demonstrated to perform quality assurance of clinical $^{192}$Ir HDR brachytherapy procedures, providing comparable dose measurements as thermo-luminescent dosimeters and accuracy within 20% of the treatment planning software (TPS) for 27 treatments conducted, with an inter-quartile range ratio to the TPS dose value of $(1.02-0.94=0.08)$. After removing contaminant signals (Cerenkov and diode background), calibration of the detector enabled accurate dose measurements for vaginal applicator brachytherapy procedures. For $^{192}$Ir use, energy response changed by a factor of 2.25 over the SDD values of 3 to 9 cm; however a cap made of 0.2 mm thickness silver reduced energy dependence to a factor of 1.25 over the same SDD range, but had the consequence of reducing overall sensitivity by 33%.

For preclinical measurements, dose accuracy of the NanoFOD was within 1.3% of MOSFET measured dose values in a cylindrical mouse phantom at 225 kV for x-ray irradiation at angles of 0, 90, 180, and 270°. The NanoFOD exhibited small changes in angular sensitivity, with a coefficient of variation (COV) of 3.6% at 120 kV and 1% at 225 kV. When the NanoFOD was placed alongside a MOSFET in the liver of a sacrificed mouse and treatment was delivered at 225 kV with 0.3 mm Cu filter, the dose difference was only 1.09% with use of the 4x4 cm collimator, and -0.03% with no collimation. Additionally, the NanoFOD utilized a scintillator of 11 $\mu m$ thickness to measure small x-ray fields for microbeam radiation therapy (MRT) applications, and achieved 2.7% dose accuracy of the microbeam peak in comparison to radiochromic...
film. Modest differences between the full-width at half maximum measured lateral dimension of the MRT system were observed between the NanoFOD (420 \( \mu m \)) and radiochromic film (320 \( \mu m \)), but these differences have been explained mostly as an artifact due to the geometry used and volumetric effects in the scintillator material. Characterization of the energy dependence for the yttrium-oxide based scintillator material was performed in the range of 40-320 kV (2 mm Al filtration), and the maximum device sensitivity was achieved at 100 kV. Tissue maximum ratio data measurements were carried out on a small animal x-ray irradiator system at 320 kV and demonstrated an average difference of 0.9% as compared to a MOSFET dosimeter in the range of 2.5 to 33 cm depth in tissue equivalent plastic blocks. Irradiation of the NanoFOD fiber and scintillator material on a \(^{137}\)Cs gamma irradiator to 1600 Gy did not produce any measurable change in light output, suggesting that the NanoFOD system may be re-used without the need for replacement or recalibration over its lifetime.

For small animal irradiator systems, researchers can deliver a given dose to a target organ by controlling exposure time. Currently, researchers calculate this exposure time by dividing the total dose that they wish to deliver by a single provided dose rate value. This method is independent of the target organ. Studies conducted here used Monte Carlo particle transport codes to justify a new method of dose prescription in mice, that considers organ specific doses. Monte Carlo simulations were performed in the Geant4 Application for Tomographic Emission (GATE) toolkit using a MOBY mouse whole-body phantom. The non-homogeneous phantom was comprised of 256x256x800 voxels of size 0.145x0.145x0.145 mm\(^3\). Differences of up to 20-30% in dose to soft-tissue target organs was demonstrated, and methods for alleviating these errors were suggested during whole body radiation of mice by utilizing organ specific and x-ray tube filter specific dose rates for all irradiations.

Monte Carlo analysis was used on 1 \( \mu m \) resolution CT images of a mouse femur
and a mouse vertebra to calculate the dose gradients within the bone marrow (BM) compartment of mice based on different radiation beam qualities relevant to x-ray and isotope type irradiators. Results and findings indicated that soft x-ray beams (160 kV at 0.62 mm Cu HVL and 320 kV at 1 mm Cu HVL) lead to substantially higher dose to BM within close proximity to mineral bone (within about 60 µm) as compared to hard x-ray beams (320 kV at 4 mm Cu HVL) and isotope based gamma irradiators ($^{137}$Cs). The average dose increases to the BM in the vertebra for these four aforementioned radiation beam qualities were found to be 31%, 17%, 8%, and 1%, respectively. Both in-vitro and in-vivo experimental studies confirmed these simulation results, demonstrating that the 320 kV, 1 mm Cu HVL beam caused statistically significant increased killing to the BM cells at 6 Gy dose levels in comparison to both the 320 kV, 4 mm Cu HVL and the 662 keV, $^{137}$Cs beams.
To my friends and family.
Contents

Abstract iv
List of Tables xiv
List of Figures xvii
List of Abbreviations and Symbols xxxi
Acknowledgements xxxvii

1 Introduction 1

1.1 Motivation ......................................................... 1
1.2 Radiation Therapy ............................................. 2
  1.2.1 The Early Years of Radiation Therapy ..................... 2
  1.2.2 Modern Radiation Therapy ................................. 4
  1.2.3 Brachytherapy ............................................. 5
  1.2.4 External Beam Radiation Therapy ......................... 9
1.3 Radiation Detectors ............................................ 14
  1.3.1 Overview .................................................... 14
  1.3.2 Limitations of Existing Detectors ....................... 15
  1.3.3 Optical Fiber Radiation Detectors ....................... 16

2 NanoFOD, Hardware and Software Development 18

  2.1 Introduction .................................................... 19
  2.2 Hardware Components ....................................... 23
2.2.1 Scintillation Pellet ............................................. 23
2.2.2 Optical Fiber .................................................. 25
2.2.3 Photo-diode ...................................................... 31
2.2.4 Data Acquisition (DAQ) ......................................... 34
2.2.5 Miscellaneous Hardware Design Considerations ............... 37
2.2.6 System Integration Testing ..................................... 46
2.3 Software .......................................................... 47
  2.3.1 Data Analysis and Post-Processing - Python .................... 47
  2.3.2 LabView Data Acquisition for PDF10A Diode System .......... 51

3 NanoFOD, Brachytherapy Radiation Therapy ............... 52
  3.1 Introduction ..................................................... 52
    3.1.1 Dose Equation and Mathematical Formalism .................. 53
    3.1.2 Energy Dependence for $^{192}$Ir ........................... 56
    3.1.3 Cerenkov Radiation and the “Stem Effect” ................... 60
    3.1.4 Calibration .................................................. 60
    3.1.5 Phantom Accuracy ......................................... 61
    3.1.6 Clinical Trials ............................................. 61
  3.2 Methods and Materials .......................................... 62
    3.2.1 Energy Dependence for $^{192}$Ir ........................... 62
    3.2.2 Cerenkov Radiation and the “Stem Effect” ................... 64
    3.2.3 Calibration .................................................. 65
    3.2.4 Phantom Accuracy ......................................... 73
    3.2.5 Clinical Trials ............................................. 74
  3.3 Results and Discussion .......................................... 80
    3.3.1 Energy Dependence for $^{192}$Ir ........................... 80
6 Monte Carlo, Red Bone Marrow Dose

6.1 Introduction ................................................. 151
6.2 Methods and Materials ................................. 153
  6.2.1 Digital Virtual Phantoms ............................ 153
  6.2.2 Distance Calculation ................................. 155
  6.2.3 Particle Transport Dose Simulations (Monte Carlo) .... 158
  6.2.4 Dose Analysis ..................................... 162
  6.2.5 Physical Dosimetry ................................. 163
  6.2.6 Ex-Vivo Animal Studies ............................. 167
  6.2.7 In-Vivo Animal Studies ............................. 168
  6.2.8 Clonogenic Survival ............................... 170
6.3 Results ...................................................... 170
  6.3.1 Particle Transport Dose Simulations (Monte Carlo) .... 170
  6.3.2 Clonogenic Survival Studies .......................... 178
6.4 Discussion ................................................. 179
6.5 Conclusion .................................................. 184

7 Future Work .................................................. 186

7.1 NanoFOD .................................................... 186
  7.1.1 Alternative Hardware ................................. 186
  7.1.2 Dosimetry for Imaging Applications .................. 187
  7.1.3 Dosimetry for External Beam Radiation Therapy ....... 187
  7.1.4 Phosphor Characterization ............................ 188
7.2 Small Animal Organ Dose - Monte Carlo ................... 188
  7.2.1 4D Monte Carlo Studies ............................... 188
  7.2.2 Bone Marrow Dose .................................... 188
## List of Tables

2.1 Relative comparison of photo detectors, data adapted from (Windhorst and Johansson, 1999). ........................................... 32

2.2 Technical performance specifications (manufacturer provided) of the diode hardware used for the construction of the NanoFOD systems. . 33

2.3 Technical data from manufacturer data sheets, for data acquisition hardware used to measure the PDF10A diode voltage. Sensitivity was defined in the NI manuals as the smallest change in voltage that could be detected. ................................................................. 37

2.4 Testing the ability of liquid electrical tape coating to block room light collected by the tip of the optical fiber. ................................. 44

3.1 Trends of experimental calibration values in comparison to the approximate relationship of the f-factor ratio of the nano-crystalline yttrium oxide material relative to liquid water. F-factors were computed using mass attenuation data (Boone and Chavez, 1996) at the root mean square (RMS) energy at each SDD value, and the $[N_{P,w}^{E,ref}k_Q]_i$ value was measured experimentally for $^{192}$Ir using a NanoFOD optical fiber positioned in liquid water. The reference energy for calibration was defined at 3 cm SDD. ....................................................... 68

3.2 Phantom dose template used to test accuracy of the 10 s cylinder dwell calibration method. ....................................................... 73

3.3 Prior to implementing the diode shielding and Cerenkov filtering, additional and undesirable signal was noticed in the photo-diode measured optical power from the irradiation of the NanoFOD phosphor at three distances. The “Expected ISQ” data column shows values calculated from theory, according to the inverse square exposure rate in air for a point source using the 3 cm SDD value as the reference. ............ 81
3.4 Comparison of relative ion chamber measurements from the fixture calibration method as compared to relative TG-43 along/away values. The 9 cm TG-43 value was extrapolated from the dataset in the range of 3–7 cm, since the dose tables only provided values out to a maximum of 7 cm “away”.

3.5 Patient-by-patient analysis of all of the clinical trial measurements for vaginal cylinder brachytherapy HDR treatments. AVG = average dose of all fractions for a single patient and STD = standard deviation of the dose from all fractions of a single patient. The patient number is an arbitrary identifier used to de-identify and anonymize the data, while allowing the fractions to be grouped by similar treatment geometry for each patient.

4.1 Calculated f-factor values used to convert the ion chamber readings from exposure in air to dose to an ICRU-44 tissue material. The mean energy was estimated using SpekCalc software. For 320 kV, the mean energy was estimated by extrapolating the data points for 300 kV and below.

4.2 Data comparison of the NanoFOD and micro-MOSFET at 225 kV in the cylindrical mouse phantom. The uncertainty is given as the standard deviation (σ) value of three repeat measurements. The difference column reports the percent difference of the NanoFOD and the MOSFET detectors.

4.3 Data comparison of the NanoFOD (labeled “Nano”) and micro-MOSFET at 225 kV and 80 kV in the liver of a sacrificed mouse. The uncertainty (σ) is given as the standard deviation value of three repeat measurements. The difference column reports the percent difference of the NanoFOD and the MOSFET detectors.

4.4 NanoFOD measured point dose values in a mammary tumor phantom for all setups shown in Figure 4.8. The † symbol indicates that the dose rate was below the typically quoted minimum detectable dose rate of the NanoFOD (0.05 cGy/s). The • symbol indicates that this point was not physically measured, but it can estimated that this dose would be between the dose of point ‘A’ and point ‘L’ (14.72 and 15.37 Gy). Data collected on the second day of experiments (Exp 2) was omitted from analysis because it showed substantial asymmetries in the irradiation and larger uncertainty in the calibration slope value, which were theorized to have occurred due to poor setup geometry of the mouse phantom relative to the irradiator isocenter.
4.5 Comparison of the radiochromic film measured values and NanoFOD values for the characterization of the CNT MRT x-ray irradiator system. Note, film dose rates were adjusted by -3.9% to account for differences in setup and geometry between conditions of film and NanoFOD irradiations.

5.1 Physics settings used in the Monte Carlo dosimetry simulations performed in GATE.

5.2 Manufacturer provided filters, available for the XRAD-320 machine.

5.3 Simulation results of the calculated dose prescription percent errors for comparing the resulting dose error in each organ if a uniform dose distribution is assumed according to the conventional dose prescription method. All dose errors are relative to the dose in the liver. Absolute standard error of the mean were all below ± 0.5%. For full list of standard error values, see (Belley et al., 2014).

6.1 Physics lists used for the Monte Carlo particle transport simulations.

6.2 Experimental radiation conditions used for the in-vivo and the in-vitro studies on the x-ray and gamma type irradiators.

6.3 Monte Carlo parameters and microdosimetry results for the 5 µm digital virtual phantoms of the femur and vertebra.

6.4 Microdosimetry results of the absolute dose values to the BM.
List of Figures

2.1 Representation of the NanoFOD optical fiber and phosphor size relative to some other commercial detectors and a US quarter. Ruler shown to provide cm scale. ................................. 20

2.2 Hardware components assembled to form the NanoFOD system. The yttrium oxide nanocrystalline scintillator material exhibited linear response under x-ray excitation (Stanton et al., 2014). Using this phosphor in the construction of a detector system required preservation of this linear behavior through the entire cascade of sub-systems (fiber, diode, data acquisition and logging, etc.) ................................. 21

2.3 Depiction of a nano-crystalline scintillator pellet attached on the end of the NanoFOD optical fiber. ................................. 24

2.4 SEM image showing the measured thickness of the pressed pellet, formed from the nano-crystalline scintillator powder in the 1 mg/7 mm pressed pellet configuration. Measured thickness was approximately 11 \( \mu m \). Image courtesy of Brian Langloss. ................................. 25

2.5 NanoFOD fiber was visible in x-ray images, with less attenuation than larger micro-MOSFETs and ion chamber detectors. This x-ray image was acquired on the Precision X-ray XRAD-225Cx small animal image guided irradiator at 80 kV with the imaging filter (2 mm Al). The aSi CsI (Tl) flat panel detector utilized 200 micron pixel size. ................................. 26

2.6 Attenuation of 600 nm light in UV/Vis optical fiber, showing high transmission of signal out to large distances. ................................. 27

2.7 An additional length of fiber was attached to the SMA-905 end of the NanoFOD device and routed to the diode. By using these extensions, the diode was able to be located outside of the radiation therapy vaults preventing scatter and stray radiation from being detected by the diode. 28
2.8 Comparison of the diode responsivity for the femtowatt receiver (Thorlabs PDF10A) and the PM100USB power meter with the S150C diode adapter. These figures were created from data presented in the Thorlabs manuals for the respective hardware.

2.9 Stock software provided with the Thorlabs PM100USB power meter (with S150C diode) yielded inconsistent sampling rates that varied with time. Here, the software was set to sample at a rate of 20 Hz, which only rarely occurred. Actual sampling rate was found to be closer to 10 Hz for the majority of the data-points.

2.10 Optical filters (550 nm long pass shown here) were placed between the sensitive detector element of the PDF10A diode and the SMA-905 connector of the fiber. Since the nano-crystalline phosphor emissions were 611 nm, and given that Cerenkov signal was peaked in the UV/blue range, the spectral separation allowed for a long pass optical filter to transmit primary signal while selectively removing the Cerenkov light.

2.11 Hardware setup for an in-scatter measurement using a vaginal cylinder applicator with $^{192}$Ir high dose rate (HDR) treatment setup. The diode was placed in the lead pig to shield it from scatter radiation in the room.

2.12 Construction of the fibers for small animal use was performed using liquid electrical tape to coat the tip of the fiber to prevent room light from reaching the diode. (a) Shows the Nylon jacketed NanoFOD fiber without any coatings on the tip, (b) shows the tip of the fiber after the application of the white liquid electrical tape coating, (c,d) show the finalized NanoFOD with one coat of white and one coat of black liquid electrical tape.

2.13 NanoFOD optical fiber assembly constructed using two different medical grade heat shrink components. The diameter was less than 0.9 mm at the distal end of the fiber, reduced from the original prototype diameter of 2.7 mm when the HS-714 shrink wrap was used for the entire fiber.
2.14 (a) Electrical components and grounding method used for the PDF10A diode, as assembled on the mobile cart. (b) Fourier transform of the raw diode voltage acquired using an oscilloscope (Agilent/Keysight DSOX2024A). Prior to grounding the SMA of the diode, substantial noise signal (-21.7 dBV) was visible at 60 Hz, induced when the diode was near any electronics connected to 120 VAC power from wall outlets. This noise was markedly reduced (to -49.9 dBV) by grounding the SMA-905 connector of the PDF10A diode to the diode chassis, and connecting to the ground reference of the Tripp-Lite circuit breaker. After grounding, the average root-mean-square (RMS) noise was below -60 dBV (1 mV RMS) for most frequencies and more closely resembled uniform white noise.

2.15 Flow chart of the software developed in Python, enabled automatic processing of batches of output files when using the PM100USB and S150C diode system. The cumulative light output for the regions displayed by yellow, was $8.317 \times 10^{-11}$ J.

2.16 Flow chart of software developed in Python, enabled data to be reduced and displayed to the user for interactive analysis of the dataset from the PDF10A diode. Final dose was 656.8 cGy for this treatment, representing the cumulative value for the region highlighted in red.

2.17 Screen-shot of the LabView program front-end GUI for the clinical NanoFOD software that was developed to acquire and display real-time signal from a treatment. The treatment displayed here, shows an actual clinical patient measurement from a tandem and ovoid treatment with two needles (Vienna applicator). Data was acquired at 50 Hz.

3.1 $^{192}$Ir energy as a function of radial distance in liquid water. Data adapted from (Baltas et al., 2006), found from Monte Carlo (MCNP) analysis of a point source placed in an 80 cm radius liquid water phantom.

3.2 Attenuation coefficients for water, silver, and tungsten in the energy range relevant to $^{192}$Ir. Deviation of the upper curves relative to that of water demonstrates that for low energy photons, the k-edge photoelectric absorption probability dominates in the high-Z materials. Figure was generated in XMuDat, using material data published by Boone (Boone and Chavez, 1996).
3.3 (a) Conceptual design of the tungsten cap hardware (not shown to scale) with wall thickness of 0.2 mm. Machine shops contacted were unable to fabricate this hardware using tungsten (Z=74), so the actual hardware piece (b) was fabricated using silver; a more easily machinable element, also with a relatively high Z number (Z=47). 63

3.4 Calibration of the first generation (2.7 mm diameter) NanoFOD device was performed by using Tegaderm Film (3M, Saint Paul, MN) to attach the NanoFOD to the side of the vaginal cylinder applicator (a). The applicator was then submerged in a water bath (b), to simulate the scatter and radiation environment encountered in a patient and according to TG-43 dosimetry protocol formalism, which calculates dose to water. 64

3.5 Expected signal with proper implementation of the Cerenkov filter. The signal should increase to a maximum value, when the SDD was a minimum. Step pattern should result due to the discrete source dwell positions. 65

3.6 Experimental setup for the earliest $^{192}$Ir HDR NanoFOD studies performed, in which the fiber was connected to the PM100USB/S150C diode. No Cerenkov filtering was used and the diode was not shielded for these studies. 66

3.7 (a) Calibration setup of the second generation miniaturized NanoFOD (0.9 mm diameter) attached to a 3 cm diameter cylinder and immersed in water. (b) CT image used to derive dose rate values in the treatment planning software (TPS). (c) Cylinder method calibration curve of the NanoFOD system. The $^{192}$Ir source (8.258 Ci) was stepped through 10 s (10 Ci planned) dwells along the length of the cylinder applicator. 67

3.8 (a) Drawing and tolerances used for the design of the calibration jig hardware, (b) rendered 3D visualization of the calibration jig concept, and (c) assembled calibration jig hardware submerged in a water tank for calibration measurements of NanoFOD alongside an ion chamber. This water tank met the recommendation of Baltas (Baltas et al., 2006) to use 24 cm of water to generate full scatter conditions necessary to accurately replicate dose reconstruction using the TG-43 dosimetry protocol. 72

3.9 Treatment plan used for the first clinical NanoFOD measurement in the first patient treated on the study. The dose template was planned to deliver 4 Gy to 0.5 cm depth, using a 4 cm length template and a 3 cm diameter stump. 75
3.10 NanoFOD and TLDs were attached with radial symmetry to a location that corresponded to roughly the central dwell channel of the $^{192}$Ir source. The $^{192}$Ir source stepped through the dwells in increments of 5 mm steps, leading to changes in the source-detector-distance with time due to the fixed geometry of the NanoFOD and TLD. Thus, real time signal tracings of the NanoFOD displayed a discrete step function relative to time, with a maximum signal when the SDD value was a minimum.

3.11 Eclipse TPS interface showing the CBCT images of the patient with the cylinder applicator positioned in the vaginal vault. The dose template has been added to the images, allowing for the visualization of the isodose lines and the calculation of the TPS dose measurement at the locations of the TLDs and NanoFOD system.

3.12 (a) The first clinical NanoFOD device, after sanitation, and ready for use in the first patient. Post treatment, a CT image was acquired of the NanoFOD optical fiber attached to the side of the cylinder during calibration in a water bath. A sizable air pocket was visible in the CT images (b), created due to the over-sized shrink wrap used as the physical barrier in the first generation NanoFOD.

3.13 Preparation of the vaginal cylinder applicator showing fixation of the Flexi Needle via Tegaderm, to locate the tip of the fiber at 12 cm distance from the base.

3.14 The NanoFOD system on the mobile cart unit, inside of the HDR treatment room. The cylinder and NanoFOD assembly is shown, with the diode inside of the shielded lead pig. The computer display shows the data from a cylinder patient measurement that was just completed.

3.15 Acquired NanoFOD signal after shielding the diode, prior to implementing the Cerenkov filter. 3.5 cm diameter cylinder applicator was used, with setup and geometry as shown in Figure 3.4. The signal was expected to be symmetric, with maximum voltage achieved at the minimum source detector distance (SDD) as the source translated along the central axis of the cylinder. Collected data deviated from the expected signal and signal generation via the fiber itself was observed, suggesting that Cerenkov may be contributing to the measured signal. Three different filtering techniques were investigated for smoothing the raw data, as shown here.

xxi
3.16 Data before (a) and after (b) implementing the optical Cerenkov filter. Signal was acquired using 10 s dwells spaced at 5 mm along the central axis of a vaginal cylinder applicator. Note, changes in signal level between (a) and (b) were due to many factors, such as the use of a different NanoFOD fiber and differences in $^{192}$Ir source activity on the day of each experiment. After implementing the Cerenkov filter, (b) data showed good agreement to the expected signal, depicted in Figure 3.5.

3.17 Monte Carlo analysis results, looking at the root mean square (RMS) detected energy inside of a given shielded cap thickness of specified material. The tungsten (W) material was found to be a superior material compared to silver (Ag) for the same thickness of material.

3.18 Calibration setup (a) with the tip of the NanoFOD placed at 11 cm distance from the base of the cylinder. The NanoFOD named C6 used the 0.2 mm thick silver cap on a 2.3 cm diameter vaginal cylinder applicator. Calibration data (b) showed good overlap of TPS measured dose (10 Ci, 10 s planned dwells) relative to the NanoFOD signal voltage. TPS marker was shifted 2 mm, since visualizing the location of the phosphor was impossible due to the high-Z metal artifact in the CT images caused by the silver.

3.19 Calibration performed using the silver cap on fiber “C6” using the acrylic test fixture designed to provide in water measurements at 3, 5, 7, and 9 cm SDD. With the silver cap, the absolute calibration factor increased by more than 60%, indicating less overall light was generated in the phosphor per unit dose as was measured by an ion chamber (Model: TN30006. PTW, Freiburg, Germany). The uncertainty in the calibration values was highest at the 3 cm location, due to uncertainties in positioning; small errors in $dr$ at small SDD lead to the largest errors due to the steep dose gradients close to the source. Uncertainties were estimated using Table 7.3 in Baltas (Baltas et al., 2006), which states that at $r=5$ cm, an uncertainty of 0.5 mm in radial positioning can lead to an uncertainty of 2.00% dose.

3.20 Calibration data and trend line fit of the NanoFOD “C6” fiber using the cylinder calibration method (source steps of 5 mm using 10 s nominal dwells). Calibration data was obtained via comparison of the NanoFOD voltage to TPS dose values at each SDD.
3.21 The calibration jig was first validated by comparing measurements of the ion chamber to the NanoFOD, using a free-in-air geometry setup. The relationship between these two sets of measurements was highly linear ($R^2=0.9998$) indicating that the manufacturing tolerances used provided accurate positioning of the NanoFOD relative to the ion chamber. Measurements were acquired at 3, 5, 7, and 9 cm SDD. 

3.22 Over-response of the raw NanoFOD voltage relative to the ion chamber measurements for increasing SDD, demonstrated the energy response of the NanoFOD in liquid water. “C10” and “C11” were the names of the two clinical NanoFOD fibers.

3.23 Recorded net voltage of clinical fibers named “C10” and “C11” as a function of distance, acquired using the calibration test fixture for $^{192}$Ir. Voltage was scaled to represent signal from a 10 Ci nominal source strength.

3.24 TG-43 based dose rates to water for radial distances from the source matching the corresponding SDD values at which the NanoFOD was calibrated at using the calibration fixture. Scaled values (extrapolated out to 9 cm) were adapted from Table XVII in AAPM/ESTRO report #229 (Perez-Calatayud et al., 2012). Absolute doses were obtained by scaling the 3 cm data point to the absolute dose rate value taken from Eclipse clinical TPS at 3 cm SDD.

3.25 Axial CT image of the first patient measurement with the cylinder applicator in place in the vaginal vault. The air pocket created by this over-sized shrink wrap would in theory, allow the tip of the fiber free movement within the range of doses shown. Dose markers, shown here from a screen-shot of Eclipse, characterized the dose gradient across this air pocket to range from about 5.9 to 7.6 Gy, over a distance of just 2.5 mm. Thus, a positioning error of 2.5 mm was shown to lead to a potential dose difference of more than 25% at the possible locations of the NanoFOD phosphor for the first patient.

3.26 (a) Raw data and the corresponding (b) smoothed data from a vaginal applicator NanoFOD patient data measurement. The real time diode voltage was plotted as a function of time, providing knowledge of the scintillator light output throughout the entire brachytherapy procedure. The finite dwells of the source were visible as the discrete steps in the tracing.
3.27 Processed clinical vaginal applicator NanoFOD dose measurement using the fixture calibration method combined with the TG-43 dose relationship in water. This figure shows the real time dose rate delivered at any given time from the brachytherapy treatment procedure. The cumulative dose value is shown here as $\int y \, dx = 697.061$ cGy. The red shaded region selects the time interval to compute the cumulative dose, and it could be selectively resized and moved via interactive user input.

3.28 Data from the vaginal cylinder clinical trial showing comparison of the NanoFOD and TLD dosimeters.

3.29 All individual NanoFOD dose fraction data plotted as a function of the source activity on the day of the measurement. The two clinical NanoFOD fibers used were arbitrarily named “C10” and “C11”.

4.1 Tissue equivalent block phantom geometry enabled increasing quantities of blocks to be stacked above the detector positions, effectively increasing the tissue attenuation depth. The tissue maximum ratio (TMR) measurements were obtained using this setup, since the source detector distance was kept constant for all measurements.

4.2 Effective point of measurement of the NanoFOD was located at the same distance from the x-ray tube as the effective point of measurement of the ion chamber. This calibration was conducted using the XRAD-225Cx with the x-ray tube positioned directly above the table (shooting top down).

4.3 NanoFOD calibration on the XRAD-225Cx was performed free-in-air, alongside a MOSFET and ion chamber detector. (Right) The placement of the NanoFOD and MOSFET were slightly below the effective point of measurement of the ion Chamber (center). Future experiments were performed with the NanoFOD SDD at the same value as the effective point of measurement of the ion Chamber (TG-61 definition of effective point of measurement).

4.4 Geometry used for the angular measurements performed in the acrylic phantom.

4.5 (Left) Planar x-ray image of the NanoFOD and MOSFET placed in the center of a cylindrical mouse phantom ($2\,cm$ diameter). (Right) Photograph of the 4x4 cm collimator installed on the x-ray tube of the XRAD-225Cx.
4.6 Planar x-ray image on the XRAD-225Cx showing side-by-side placement of the NanoFOD and Micro-MOSFET in the liver of a sacrificed mouse. .......................... 112

4.7 (a) X-ray radiograph showing the location of the NanoFOD in the mammary tumor phantom. (b) Photograph of the NanoFOD fiber located in the mammary tumor phantom setup on the treatment stage of the XRAD-225Cx. .......................... 113

4.8 Geometry used for placement of the NanoFOD in various positions of the mammary tumor and the mouse body, with both open field and blocked field setups. Each point dose measured was represented by a letter, “A” through “L” for keeping track of the values. ............... 114

4.9 Schematic of the scan geometry showing relative orientation of the inorganic scintillation material and the optical fiber detector relative to the x-ray field. Dimensions and geometry of the collimated microbeam are also depicted. Note, diagram not shown to scale. ............... 115

4.10 The optical fiber (NanoFOD) detector was placed along the Z-axis of the cylindrical mouse phantom. The mouse phantom was then clamped (green hardware) to a translational stage, to enable motion in a direction perpendicular to the long axis of the microbeam. The stage moved from right-to-left, enabling the smallest dimension of the scintillator pellet to be used to measure the microbeam width. ...... 118

4.11 TMR data for three different detectors in a tissue equivalent block phantom, under 320 kV x-ray irradiation. .................... 120

4.12 NanoFOD sensitivity characterized over a range of x-ray tube potentials. Maximum light output per unit dose was achieved just below an average x-ray energy of 50 keV, at an x-ray tube potential of 100 kVp. 120

4.13 Linear calibrations of the NanoFOD system with the PDF10A diode achieved by varying the tube current at two x-ray energies on the XRAD-320, using 2 mm aluminum added filtration. No saturation of detector signal or loss of linearity was observed even for dose rates in excess of 2 Gy/min. 2 Gy/min likely represents the upper limit of dose rates used for small animal studies on these irradiators. ...... 121

4.14 Data for the angular response of the NanoFOD system about two different axes at 120 kV. .......................... 122

xxv
4.15 Calibration data for the NanoFOD use on the XRAD-225Cx at two energies, using the Thorlabs PM100USB/S150C diode (y-axis units are calibrated to energy from the manufacturer). The $R^2$ value was $>0.9999$ for both cases, after fixing the y-intercept to 0. . . . . . . . . 123

4.16 Linearity data of the calibration compared across the four experiments, showing two fibers that each exhibited changes in calibration. Due to large uncertainty in the calibration data for the second experiment (Exp 2), this data was omitted from the analysis and the results from the dosimetry are not reported here. . . . . . . . . . . . . . . . 125

4.17 NanoFOD integrated optical power response characterized over a range of cumulative 160 kV x-ray exposures on the UNC CNT microbeam system. The collimation was removed during calibration to enable side-by-side irradiation of the NanoFOD and ion chamber. . . . . . . . . . . . . . . . 127

4.18 Raw (black) and smoothed diode data (red) resulting from the scanning of the x-ray microbeam with the NanoFOD system. Axes shown in blue represent calculated values, after applying calibration for dose rate (right axis) and the translation stage movement speed to find the position (top axis). Time 0 s indicated the right edge of the x-ray beam, and time 300 s represented the left edge. . . . . . . . . . . . . . . . 128

4.19 Characterized lateral beam profile of the x-ray microbeam from the UNC CNT MRT system. Data displayed here was smoothed using a rectangular filter with width of 0.55 s. . . . . . . . . . . . . . . . . . 129

4.20 Depiction of the volumetric effects of partial irradiation of the scintillation volume and geometry dependent effects due to the angle of the microbeam. Spatial changes in sensitivity and light collection via the optical fiber were not accounted for during calibration, as calibration was provided by irradiation of the entire scintillator volume. . . . . . . 131

4.21 Data from the $^{137}$Cs lifetime test, conducted by delivering protracted radiation exposure to the NanoFOD alongside an ion chamber. Cumulative dose delivered was in excess of 1600 Gy. . . . . . . . . . . . 132

5.1 MOBY mouse phantom renderings. 3 cross-plane views and 3D rendering created from the x-ray CT attenuation data provided as output from the MOBY software. . . . . . . . . . . . . . . . . . 136

5.2 The MOBY phantom was used to define the (a) material definitions for dosimetry derived from photon attenuation data, (b) anatomical definitions of organs derived from the source activity output, and (c) corresponding organ masks such as the lung mask. . . . . . . . . . . . 139
5.3 Relative energy spectra, showing relative beam hardening as more filtration was used. Data was obtained from simulations performed using Geant4 and for $10^8$ source particles. Data was re-binned in groups of five to create this figure.

5.4 Physical HVL measurements performed on the XRAD-320 with an ion chamber and high purity copper filters. Beam attenuation curves are shown for beams using filters A, B, and C. The black dotted line shows 50% attenuation, indicating the thickness of material necessary to achieve one HVL.

5.5 Dose distribution in the central coronal slice of the 33 g MOBY mouse phantom for (a) filter A, (b) filter B, and (c) filter C. Reported doses were normalized per $1 \times 10^9$ source particle histories (emitted photons from x-ray tube).

5.6 Relative organ dose values obtained from Monte Carlo simulation results in MOBY mouse phantom for three different (filter A, B, C) x-ray spectra produced from the XRAD-320. Relative dose values were found to be nearly independent of the mouse size within the range of sizes studied: (a) 12 g, (b) 23 g, and (c) 33 g. Doses shown here were normalized to the maximum organ dose, found to occur in skeletal mineral bone tissue.

5.7 Cylindrical mouse phantom (made of tissue equivalent plastic) shown here with a micro MOSFET inserted along the central axis. The laser shows the central location of the XRAD-320 field.

6.1 Scout images of the femur and vertebra obtained from the SCANCO CT system. Demarcations shown on femur for regions of the trabecular rich metaphysis and trabecular poor diaphysis.

6.2 Axial images from the 1 $\mu$m resolution SCANCO CT scans of the (a) femur and (b) vertebra. Since the bones were stored in ethanol prior to scanning, the trabeculae had to be contoured to define regions of the anatomy that contained BM. Note - images not shown to scale.

6.3 Planar images of the final virtual phantoms derived from the 1 $\mu$m SCANCO CT images. The final phantoms used in the dosimetry simulations were down-sampled to 5 $\mu$m isotropic voxel size for both the mouse vertebra (left) and femur (right).
6.4 (a) The three-region vertebra phantom of bone (white), BM (gray), and outside regions (black) created from the 1 μm SCANCO CT images. (b) Distance results displayed as a contour map, representative of the distance of each BM voxel to the nearest cortical bone structure computed according to software developed in Python.

6.5 X-ray spectra used for the dosimetry simulations. Three distinct beam qualities were studied, with varying levels of filtration. All utilized a tungsten anode material. The 320 kV beams were obtained using Geant4 based on XRAD-320 geometry, and the 160 kV beam was obtained using SpekCalc. The area under the curves were normalized for display purposes.

6.6 Depiction of the macrodosimetry study geometry, of the 137Cs irradiation of the MOBY mouse, with 5 mm acrylic buildup material. The acrylic material thickness was representative of the container used for irradiating the mice on the 137Cs irradiator. Note - this image is not shown to scale.

6.7 Calibration setup, using acrylic holder to position a batch of TLD-100 chips around a 6 cm³ ion chamber. Chips were irradiated using 320 kV tube potential provided by the XRAD-320, at two distinct beam qualities of 1 mm Cu and 4 mm Cu HVL.

6.8 Cell plates were located on the floor of the 137Cs irradiator. The grid pattern was used to map out the dose rates as a function of distance from the source. The sheets of lead (visible in the back) provided attenuation of the gamma rays to achieve a lower dose rate. The cell plates were placed on the floor of the irradiator to obtain oblique angles of radiation through the bone equivalent material.

6.9 XRAD-320 irradiation geometry for the 1 mm Cu HVL beam. Styrofoam blocks were used to select specific SSD values for the cell plates. The wells containing cells were positioned along the central axis of the x-ray irradiator.

6.10 Histograms of bone marrow distance to cortical bone for different anatomical locations within mouse bones. Distances were calculated using an algorithm developed in Python, and all data was processed based on the anatomy of the digital virtual phantoms created from the 1 μm resolution CT images from SCANCO. This dataset represents $P(x)$ from Equation 6.1.
6.11 Percent depth dose plots in the MOBY mouse phantom for different x-ray beam qualities on orthovoltage irradiators and for $^{137}$Cs gamma irradiation. (a) Displays full depth dose curves and (b) shows the first 3 mm of data to highlight the differences in buildup at shallow depths for the $^{137}$Cs beams with and without buildup material. . . . . . . . 172

6.12 (a) Rendered image of the skeletal anatomy using the 25 µm resolution CT dataset from the C57BL/6 mouse in which the lumbar vertebrae and femur were harvested from (highlighted in red). (b) Heat map of the dose distribution throughout the MOBY mouse whole body phantom from x-ray irradiation at 320 kV, 1 mm Cu HVL. Output from Monte Carlo simulation of $1 \times 10^8$ source particle histories, rendered into a 3D view using the AMIDE VolPack volume rendering library (shear-warp factorization technique). . . . . . . . . . . . . . . . . . . 173

6.13 Histogram of the Monte Carlo microdosimetry data displaying the volume of BM receiving a given dose ratio for different photon beam energies. Dose ratio was defined here as the ratio of the dose to the BM relative to the dose to the BM at distances greater than 100 µm from mineral bone. Figure legends display the average value over the entire BM compartment. Separate anatomical regions were analyzed according to the (A) diaphysis of the femur, (B) distal metaphysis of the femur, and (C) vertebra. . . . . . . . . . . . . . . . . . . . . . . 176

6.14 Microdosimetry Monte Carlo results analyzed to display relation of the relative bone marrow dose as a function of the distance from mineral bone. Two separate regions of the femur were separately analyzed to assess effects of anatomy on the BM dose. Overall, similar dose gradients were found to occur in both the diaphysis and the metaphysis of the femur. The reader is reminded that the fractional volume of bone marrow at a given distance from bone is drastically different in these two regions, leading to large differences in the overall dose absorbed. This dataset represents $D(x)$ from Equation 6.1. . . . . . . . 177

6.15 Additional depth-dose data plots for the vertebra and distal metaphysis of the femur. Results are similar to those shown in Figure 6.14. This dataset represents $D(x)$ from Equation 6.1. . . . . . . . . . . . . . . . . . . . . . . . . . 178
6.16 In-vitro data of the clonogenic survival fraction of hematopoietic progenitor (CFU-C) cells exposed to 6 Gy relative to an un-irradiated control group. Using the Mann-Whitney U-test ($p < 0.05$), a statistically significant decrease in survival was observed at the lowest energy beam quality condition when the cells were placed on the BEM in comparison to when no BEM was used, due to dose enhancement of the photoelectrons generated at the interface.

6.17 In-vivo data of the clonogenic survival fraction of myeloid progenitor (CFU-GM) and pre colony forming erythroid progenitor (BFU-E) cells harvested 24-hours post irradiation, from mice exposed to 6 Gy relative to an un-irradiated control group. Using the Mann-Whitney U-test ($p < 0.05$), a statistically significant decrease in survival was observed at the lowest energy beam quality condition compared to the higher energy radiations of 4 mm Cu HVL at 320 kV and $^{137}\text{Cs}$. . . . 180
List of Abbreviations and Symbols

Symbols

\( A \)  Mass Number, \( A=Z+N \).
\( a_s \)  Source Activity.
\( \beta^- \)  Beta Minus Radiation.
\( B \)  NanoFOD Background Signal.
\( ^{60}\text{Co} \)  Cobalt, Radioactive Isotope (\( A=60 \)).
\( ^{137}\text{Cs} \)  Cesium, Radioactive Isotope (\( A=137 \)).
\( C_O \)  Organ Specific Correction Factor.
\( d_n \)  Source Detector Distance, for Source Dwell Position ‘n’.
\( D \)  Dose.
\( D_T \)  Target Dose.
\( D_{T,O} \)  Target Dose, to a Specific Organ.
\( \dot{D}(r, \theta) \)  2D Dose-Rate Distribution from AAPM TG-43.
\( \dot{D}_M \)  Measured Dose Rate.
\( D_w \)  Dose to Water.
\( E \)  Energy.
\( e \)  Electron Charge.
\( eV \)  Electron Volt.
\( f \)  Roentgen to Dose Conversion Factor, Known as “F-factor”.
\( F(r, \theta) \)  TG-43 Anisotropy Function.
\( g_L(r) \)  
TG-43 Radial Dose Function (Line Source Approximation).

\( G \)  
NanoFOD Gross Signal.

\( G_L(r, \theta) \)  
TG-43 Geometry Function (Line Source Approximation).

\( ^{192}\text{Ir} \)  
Iridium, Radioactive Isotope (A=192).

\( k_{\text{appl}} \)  
Applicator and Catheter Attenuation Correction Factor.

\( k_{\text{ion}} \)  
Ion Recombination Correction Factor.

\( k_{m,w} \)  
Detector Perturbation Correction Factor, Medium vs. Water.

\( k_P \)  
Pressure Correction Factor.

\( k_Q \)  
Beam Quality Correction Factor.

\( k_T \)  
Temperature Correction Factor.

\( k_V \)  
Volume Correction Factor.

\( k_{wp} \)  
Phantom Material to Liquid Water Correction Factor.

\( m \)  
Mass.

\( M \)  
Detector Measurement.

\( N \)  
Neutron Number, N=A-Z.

\( N_w \)  
Chamber Calibration Factor (Generally for \(^{60}\text{Co}\)).

\( N_{D,\text{ref}}^{E_{\text{ref}}} \)  
NanoFOD Calibration Factor, For Reference Energy.

\( nC \)  
Nano Coulomb.

\( R \)  
Responsivity.

\( r_b \)  
Bend Radius.

\( r_f \)  
Fiber Radius.

\( S_K \)  
Air Kerma Strength.

\( t \)  
Time.

\( T_{1/2} \)  
Half Life.

\( V \)  
Voltage.

\( w_T \)  
Tissue Weighting Factor, ICRP Notation.
$x$ Position Coordinate.

$z$ Position Coordinate.

$Z$ Atomic number, $Z=A-N$.

$\beta$ Speed, $\beta = v/c$.

$\eta$ Refractive Index, Also 'n'.

$\Delta \eta$ Refractive Index Difference, Core and Cladding.

$\Delta_M$ Difference in Index Values from BM Voxel to Mineral Bone Voxel.

$\lambda$ Wavelength.

$\Lambda$ TG-43 Dose Rate Constant.

$\theta$ Angle Coordinate.

$\Psi$ Angle Coordinate.

$\rho$ Mass Density.

$\mu$ Linear Attenuation Coefficient.

Abbreviations

2D Two Dimensional.

3D Three Dimensional.

3DCRT 3D Conformal Radiation Therapy.

AC Alternating Current.

ADCL Accredited Dosimetry Calibration Lab.

ARS Acute Radiation Syndrome.

aSi Amorphous Silicon.

AWG American Wire Gauge.

CCD Charge Coupled Device.

$CF$ Correction Factor.

CNT Carbon Nano-Tube.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>COTS</td>
<td>Commercial Off-The-Shelf.</td>
</tr>
<tr>
<td>COV</td>
<td>Coefficient of Variation, $COV = \frac{\sigma}{\bar{x}}$.</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid.</td>
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<tr>
<td>CT</td>
<td>Computed Tomography.</td>
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<tr>
<td>DAQ</td>
<td>Data Acquisition.</td>
</tr>
<tr>
<td>dBV</td>
<td>Decibels, Relative to 1 Volt.</td>
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<tr>
<td>DMM</td>
<td>Digital Multimeter.</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid.</td>
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<tr>
<td>EC</td>
<td>Electron Capture.</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration.</td>
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<tr>
<td>FOV</td>
<td>Field of View.</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full Width, at Half Max.</td>
</tr>
<tr>
<td>GATE</td>
<td>Geant4 Application for Tomographic Emission.</td>
</tr>
<tr>
<td>GUI</td>
<td>Graphical User Interface.</td>
</tr>
<tr>
<td>HBA</td>
<td>Homogeneous Bone Approximation.</td>
</tr>
<tr>
<td>HDR</td>
<td>High Dose Rate, 12 Gy/h at Prescription Point (TG-59).</td>
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<tr>
<td>HVL</td>
<td>Half Value Layer.</td>
</tr>
<tr>
<td>ICRP</td>
<td>International Commission on Radiological Protection.</td>
</tr>
<tr>
<td>ID</td>
<td>Inside Diameter.</td>
</tr>
<tr>
<td>IGRT</td>
<td>Image Guided Radiation Therapy.</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy.</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board.</td>
</tr>
<tr>
<td>ISQ</td>
<td>Inverse Square.</td>
</tr>
<tr>
<td>kV</td>
<td>Kilo-voltage, Constant Potential Generator.</td>
</tr>
<tr>
<td>kVp</td>
<td>Peak Kilo-voltage, Non-Constant Potential Generator.</td>
</tr>
<tr>
<td>LINAC</td>
<td>Linear Accelerator.</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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</tr>
<tr>
<td>LSI</td>
<td>Linear Shift Invariant.</td>
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<td>MFP</td>
<td>Mean Free Path.</td>
</tr>
<tr>
<td>MLC</td>
<td>Multi-Leaf Collimator.</td>
</tr>
<tr>
<td>MOSFET</td>
<td>Metal Oxide Semiconductor Field Effect Transistor.</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging.</td>
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<tr>
<td>MRT</td>
<td>Microbeam Radiation Therapy.</td>
</tr>
<tr>
<td>MV</td>
<td>Mega-voltage.</td>
</tr>
<tr>
<td>NA</td>
<td>Numerical Aperture.</td>
</tr>
<tr>
<td>NanoFOD</td>
<td>Nano-crystalline-scintillator Fiber Optic Detector.</td>
</tr>
<tr>
<td>OEM</td>
<td>Original Equipment Manufacturer.</td>
</tr>
<tr>
<td>OH</td>
<td>Hydroxyl, Chemical Group.</td>
</tr>
<tr>
<td>PDD</td>
<td>Percent Depth Dose.</td>
</tr>
<tr>
<td>PET</td>
<td>Polyethylene Terephthalate.</td>
</tr>
<tr>
<td>PIN</td>
<td>Semiconductor Junction, P-Type and N-Type with Intrinsic Region.</td>
</tr>
<tr>
<td>PMMA</td>
<td>Poly(methyl methacrylate).</td>
</tr>
<tr>
<td>PMT</td>
<td>Photomultiplier Tube.</td>
</tr>
<tr>
<td>PN</td>
<td>Semiconductor Junction, P-Type and N-Type.</td>
</tr>
<tr>
<td>POF</td>
<td>Plastic Optical Fiber.</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts Per Million.</td>
</tr>
<tr>
<td>PSF</td>
<td>Point Spread Function.</td>
</tr>
<tr>
<td>PV</td>
<td>Photo-Voltaic.</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance.</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative Biological Effect.</td>
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<tr>
<td>RBM</td>
<td>Red Bone Marrow.</td>
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<tr>
<td>RIA</td>
<td>Radiation Induced Attenuation.</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>RMS</td>
<td>Root Mean Square.</td>
</tr>
<tr>
<td>RT</td>
<td>Radiation Therapy.</td>
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<tr>
<td>SAIGRT</td>
<td>Small Animal Image Guided Radiation Therapy.</td>
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<tr>
<td>SDD</td>
<td>Source Detector Distance.</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscope.</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio.</td>
</tr>
<tr>
<td>SSD</td>
<td>Source to Surface Distance, or Source Skin Distance.</td>
</tr>
<tr>
<td>TG-43</td>
<td>AAPM Task Group Report #43, Dosimetry of Interstitial Brachytherapy Sources.</td>
</tr>
<tr>
<td>TG-59</td>
<td>AAPM Task Group Report #59, HDR Brachytherapy Treatment Delivery.</td>
</tr>
<tr>
<td>TIR</td>
<td>Total Internal Reflection.</td>
</tr>
<tr>
<td>TLD</td>
<td>Thermo-Luminescent Dosimeter.</td>
</tr>
<tr>
<td>TMR</td>
<td>Tissue Maximum Ratio.</td>
</tr>
<tr>
<td>T&amp;O</td>
<td>Tandem and Ovoid.</td>
</tr>
<tr>
<td>T&amp;O</td>
<td>Tandem and Ring.</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra Violet.</td>
</tr>
</tbody>
</table>
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1

Introduction

1.1 Motivation

Radiation therapy, used in the fields of small animal radiation biology, radiation protection, and medicine, requires high resolution dosimetry to verify efficacy of the treatment and safety of the subject. To better understand the biological effects of radiation, the quantity of radiation dose that was delivered to a given location should first be accurately known. Novel chemistry advancements in nano-crystalline materials has enabled the construction of miniature radiation detectors which can achieve radiation measurements at resolutions that exceed the performance capabilities of most commercially available alternatives. Similarly, new computational technology can be combined with state of the art imaging modalities to perform novel particle transport dose studies on large datasets to investigate dosimetric effects in micron-scale anatomical regions of murine anatomy. The development, testing, and characterization of these tools has been pursued to advance science, by way of the production of new knowledge for applications relevant to preclinical animal studies and clinical radiation therapy.
1.2 Radiation Therapy

1.2.1 The Early Years of Radiation Therapy

The fields of radiation research and radiation protection have seen many changes over the past 120 years. To best understand the advantages afforded from rigorous scientific testing that resulted from (i) preclinical small animal radiation therapy studies and (ii) the development of novel radiation detectors, the historical progression of radiation therapy treatments should be reviewed.

The turn of the 20th century marked a new era in medicine, as physicians began experimenting with the newly discovered x-rays (1895 discovery by Röntgen). In the early 1900’s x-ray radiation, known as “Röntgen Therapy”, was believed to be a swiss army knife treatment for divers ailments including dermatological abnormalities, tuberculosis, lupus, and cancer (Williams, 1907). Physicians and scientists conducted human subject testing often with little to no knowledge of toxicity and lacking a scientifically rigorous way to quantify the radiation dose delivered (Leonard, 1905). The early use of x-rays was predicated on the belief that the short term radiation side-effects such as necrosis and dermatitis were only a temporary inconvenience of the treatment, but were tolerable in comparison to the fatality of the disease that would result in its absence (Leonard, 1907). Further, the mechanisms by which cure and the biological effects of the treatment were achieved, were unknown and highly disputed at the time (Freund, 1910; Leonard, 1907). Despite these and many more unknowns (such as the ability of radiation to induce genetic transmutations as was later discovered 1927 (Muller, 1927)), experimental x-ray treatments of the early 20th century continued to be performed in the noble quest to uncover innovative techniques that held promise and potential for new cures of disease, placing the heavy burden of risk and uncertainty directly on the patients. The consequences of this human subject testing were two-fold. Firstly, positive outcomes gave credi-
bility to the use of x-rays as an appropriate treatment technique that was found to extend both the survival and quality of life for patients suffering with diseases that were historically challenging to treat (Pusey, 1902; Leighton, 1933; Binkley, 1933). Secondly, and in contrast to the first, negative outcomes led to adverse effects such as death, pain, discomfort, dis-figuration, and loss of organ function. These adverse effects were not limited to only the research subject population, but also afflicted the scientists and physicians conducting the studies themselves as they lacked knowledge of radiation protection principles (March, 1944; Cole, 1925).

As the ideas and methods in which practiced medicine progressed, the need developed for preclinical radiation experiments to better understand the biological effects of radiation. Early on, small animals were used for this purpose, acting as surrogate organisms to model human biological systems and to study the overall radiation effects (Marinelli, 1949; AS and Apohle, 1927; Stephens and Florey, 1925). Continuing to the present day, mice and other small animals continue to be used to vigorously and scientifically conduct radiation studies to characterize toxicity, efficacy, dosing, side effects, and overall outcome (Kirkpatrick et al., 2010). Mice are well suited for preclinical radiation studies, since they are easy to handle, have an accelerated lifespan, share many similarities with the human genome (Chinwalla et al., 2002; Mural et al., 2002), and afford an easily accessible means to conduct a large sample size study on a genetically similar population via the use of inbred strains. All factors of which, allowed for statistically relevant results to be obtained as an indication for expected biological effects that would be encountered when medical radiation was used to treat and diagnose the human population. Thus, preclinical small animal radiation research alleviated the burden of risk and uncertainty that was previously carried by patients.

Additionally, radiation detectors were needed to measure the quantity and quality (energy) of radiation that was being used for these treatments. Without a careful
means to measure radiation, the dose could not be accurately and repeatably prescribed, biological response curves could not be developed to accurately characterize dose dependent radiation effects, and the treatments would have to continue to rely on the traditional biological indicators such as erythema as the primary means of controlling the length of the radiation treatment.

1.2.2 Modern Radiation Therapy

Modern day treatments, in comparison to the early 1900’s, require accurate and precise delivery of radiation. Dose prescription, spatial dose profiles and contouring, and recovery time between treatments are all important factors of modern radiation therapy treatments, and are based on scientific studies supporting evidence of improved patient outcomes (Bentzen et al., 2010). Current treatments, as they are performed at Duke, make use of modern imaging technologies such as x-ray computerized tomography (CT), positron emission tomography, and magnetic resonance imaging (MRI) to enable personalized treatments, that can be customized to individual patient anatomy, disease type, and/or progression (Chino and Secord, 2013).

The goal of modern curative radiation oncology treatments is to identify and kill cancer cells by delivering a sufficiently high dose to the target volume, while sparing dose delivery to the surrounding normal healthy tissues. The dose to the target has been shown to correlate well with the chance of cure for multiple cancer types (Urbanic and Lee, 2006; Dimopoulos et al., 2009; Olsen et al., 2011; Bartelink et al., 2007), and sub-optimal or non-compliant treatment plans have demonstrated outcomes of reduced tumor control probability (Peters et al., 2010; Ohri et al., 2013). Similarly, it has been well documented that healthy tissues exhibit dose dependent sensitivity to radiation injury (Marks et al., 2010; Georg et al., 2012; Ghafoori et al., 2008).

Successful treatments should optimize the competing requirements of staying be-
low the upper limits of normal healthy tissue dose, and attempting to meet or exceed
the lower limit of the prescribed dose to the target volume (Hamacher and Küfer,
2002). For this reason, imaging is essential to acquire information about the ex-
tent and location of the disease, as well as the relative positions of nearby healthy
organs. Contours drawn on these images are what will ultimately be used by the
treatment planning system (TPS) to optimize the treatment plan based on the input
constraints (Khan, 2010). After imaging, the patient would be re-positioned on the
treatment table for the final setup and delivery of the treatment plan. The final 3D
dose distribution delivered to the patient may be subject to errors in any phase of this
process: imaging, contouring and planning, patient setup, and treatment delivery.
3D treatments that utilize high dose and small treatment margins have the ability
to provide substantial benefit via dose sparing to organs at risk, but this comes at
the elevated possibility of missing the target (Van Herk, 2004).

1.2.3 Brachytherapy

Overview

Brachytherapy is a technique that uses a small and implantable radioactive source
to deliver interstitial or inter-cavity therapeutic radiation dose to an intended tar-
get. The main advantage of brachytherapy, is the steep dose fall-off with increasing
distances from the radioactive seed, due to the near point-source geometry. Ad-
ditionally, the small radioactive material volume can be located directly inside of
the tumor tissue, or in close proximity, to provide substantially increased dose to
the target volume while minimizing the dose delivery to normal healthy tissues at
distances far away from the source. Via the use of a machine known as a remote
afterloader, a radioactive source can be remotely moved in and out of guide wires and
catheters allowing accurate positioning of the radioactive source at known locations
within the patient’s body. Treatment plans make use of the afterloaders to define a
collection of source dwell locations and dwell times to control the superposition of dose and the resulting spatial distribution. These guide wires and catheters can be inserted in arbitrarily complex configurations and arrangements providing conformal dose contours. It should be paramount to the safety of the patient, and the efficacy of the treatment, to implement a physical detector to double check the dose delivery in real time.

For high dose rate (HDR) brachytherapy, treatment times are typically on the order of 5-15 minutes depending on the treatment plan in use, and the source activity. HDR brachytherapy employs an isotope of small size that can produce a high dose rate of at least 12 Gy/h at the prescription point (Kubo et al., 1998). Due to the complexity of the treatment, and the high stakes involved in which small errors in planning and delivery can lead to large errors in the accumulated dose, HDR brachytherapy requires the coordinated efforts of a team of dosimetrists, physicists, and physicians to collectively work together to realize high quality treatment via the use of robust quality assurance (QA) procedures. Brachytherapy often involves doses to the target that are 2-4 times larger than those used for external beam treatments, so an error in a single fraction represents a larger overall error as a percentage of the total number of treatment fractions.

Brachytherapy procedures are an essential and effective tool in the treatment and prevention of recurrence for gynecological malignancies such as cervical and uterine cancer, and have been shown to provide lower toxicity to the gastrointestinal organs as compared to external beam treatments (Gill et al., 2014; Nout et al., 2010, 2011). Gynecological treatments use two main types of clinical devices, known as applicators. Applicators are placed within the vagina or the uterus, to provide guide wires and catheters to locate the radioactive source within the patient. The first type of applicator (cylinder) is composed of a cylinder typically in the range of 2-3.5 cm diameter that is placed in the vagina during treatment. A hollow cavity
is located along the central axis of the cylinder allowing the radioactive source to step along the entire length of the cylinder, to provide a radially symmetric dose to the walls of the vagina. The second type of applicator is more complex, and is used to treat uterine and ovoid disease sites. This second applicator type makes use of either a tandem and ovoid (T&O) or a tandem and ring (T&R) treatment applicator. Additional interstitial needles can be added (to form what is known as the Vienna applicator) to extend the dose distribution to treat disease sites in the parametrial and paracervical locations.

For Brachytherapy, the relevant target volumes are defined as (Haie-Meder et al., 2005; Pötter et al., 2006):

- **GTV** Gross tumor volume. All visible disease.
- **HRCTV** High risk clinical target volume. Considered to contain macroscopic disease (dose target 75-85 Gy), this volume includes GTV, gray zones, and the cervix.
- **IRCTV** Intermediate risk clinical target volume. Considered to contain microscopic disease (dose target 60-65 Gy), this volume adds a 10 mm margin on the HRCTV, limited to only 5 mm in both the anterior and posterior directions.

*The Need for Real Time, In-Vivo Dosimeters*

Three types of treatment errors with brachytherapy are (i) human operator based such as errors in placement of radiation source or source activity strength (DeWerd et al., 2011)), (ii) equipment malfunction based such as afterloader errors in source position or dwell time, and (iii) movement of the source or equipment by some other means such as by the patient. Moreover, errors can arise from the use of the wrong treatment plan, contouring mistakes, intra-fraction organ and applicator movement, and interchanged guide tubes (Tanderup et al., 2013b). Intra-fraction changes result due to separation in time between the imaging/planning and the treatment delivery
stages, leading to potential uncertainty in delivered dose accuracy due to the movement of organs such as the kidneys (2 cm movements are possible (Bussels et al., 2003)), filling of the bowels or bladder (which can shift the target volume by up to 4 cm (Jadon et al., 2014)), and movement of the applicator. The occurrence rates for many errors and malfunctions in brachytherapy are not well known, due to insufficient data from the lack of real-time in-vivo dosimetry data.

Human error has been identified as the main cause of errors during HDR brachytherapy procedures (Ashton et al., 2005). Further, the International Commission on Radiological Protection (ICRP) report number 97 (Ashton et al., 2005) stated as a main point “Many accidents could have been prevented if staff had had functional monitoring equipment and paid attention to the results”. The need for a small size radiation detector that can provide additional knowledge and new quality assurance capabilities for these HDR treatments can not be overstated. The detector should be capable of real time in-vivo measurements to provide feedback to the clinical team, and should be implemented to prevent and/or stop treatments from occurring when an error results.

Utilization of the nano-crystalline scintillator based fiber optic detector (NanoFOD) system for HDR dose studies offers the potential to provide contemporary information about error and malfunction occurrence rates during brachytherapy. Similarly, a well designed radiation detector, would make it possible to detect organ and applicator movement as are encountered between the planning and treatment stages. Not only can generalizable knowledge be gained in these arenas, but additional interlocks could be designed to detect gross errors and halt treatment. The ability to terminate treatment before the majority of the dose has been delivered, could also allow the clinical team to perform a root cause study, and implement corrective action on the spot to repeat the treatment with the proper and accurate dose plan.
1.2.4 External Beam Radiation Therapy

Overview

In contrast to brachytherapy, external beam radiation therapy utilizes a radiation source that delivers the treatment from outside of the patient’s body. Linear accelerators (LINACs) are machines that generate high energy electron beams, and can produce either a treatment beam of electrons or photons. They utilize a gantry head that rotates around an axis known as the “isocenter”. A technique common for external beam treatments locates the target volume at the isocenter, and delivers multiple radiation beams at different gantry angles, superimposing the dose due to the treatment field overlaps that occur at the isocenter (Gardner et al., 1972). This technique thus delivers a high dose to the target volume located at the isocenter due to the summation of the individual beams, while regions outside of the isocenter are spared, due to the spreading of the remaining radiation injury over a large volume of tissue. Multiple beam, isocenter treatments are designed to deliver doses to a target volume with an allowed setup margin, and isodose contours attempt to maintain steep gradients so nearby structures outside of the treatment volume are spared (Leibel et al., 1991; Hanks et al., 1996). These treatments are known as 3D conformal radiation therapy (3DCRT) when the treatment fields are setup based on the two-dimensional projections of the target and when a uniform intensity is used across the field (Verhey, 1999).

Further, a technique in which the field shape and intensity of each individual radiation beam can be temporally manipulated, allows further control of the dose delivery (Levene et al., 1978; Convery and Rosenbloom, 1992). This technique is known as intensity modulated radiation therapy (IMRT). These IMRT techniques utilize motor controlled “leafs” in the head of the linear accelerator that can move in and out of the radiation treatment field in real time, thus blocking radiation
to create arbitrary and complex field shapes. IMRT thus provides a conformal, and highly customized dose profile that is capable of sparing nearby healthy tissue while maintaining high dose to a large volume of the intended target (Verhey, 1999; Zelefsky et al., 2001). For IMRT treatments to be most effective, they require inverse planning on the CT image dataset of the patient (Censor et al., 1988b,a). Inverse planning is a computational optimization algorithm that allows the user to input initial conditions and dose constraints, and then an iterative process determines a fluence and multi-leaf collimator (MLC) controlled treatment plan that attempts to meet these criteria.

In comparison to 3DCRT, the under-dose delivery errors that may result due to insufficient margins, setup errors, and/or motion have more severe consequences for IMRT plans (Verhey, 1999). Due to the tight tolerances and small margins used, QA is needed to verify the dose delivery for IMRT. One study found a 36% failure rate of 16 participating institutions for pelvic IMRT, in which failure was defined as dose delivered to a phantom that deviated by 7% of the planned magnitude, or exceeded 4 mm distance to agreement criteria (Ibbott et al., 2006). Again, comparing IMRT to 3DCRT, dose volume studies have demonstrated that for IMRT an increased volume of normal tissue was exposed to lower doses, which may lead to increased risk of secondary cancers for patients surviving 10 years or more (Hall and Wuu, 2003).

Use of Small Animals for Preclinical Research

Emerging technology in the field of small animal radiation therapy attempts to mimic the clinical human 3DCRT and image guided radiation therapy (IGRT) techniques. New radiation treatment machines enable novel preclinical radiation therapy research to be performed. X-ray irradiators such as the small animal radiation research platform (SARRP, Xstrahl Ltd., UK), and the XRAD-225Cx (Precision X-ray Inc, North Branford, CT) incorporate x-ray CT imaging and concurrent x-ray delivery for ther-
apy level (Gy) dose treatment of mice and small animals. Targeted and precise x-ray treatments based on image guidance is possible (Tillner et al., 2014; Verhaegen et al., 2014; Granton et al., 2012), with the capability to use sophisticated 3D treatment planning software for mice (Balvert et al., 2015; Granton, 2014).

Mice and small animals pose many significant challenges in contrast to humans, due in part to many factors such as (i) small organs, (ii) low-energy physics interactions consequential to the orthovoltage treatment machines, and (iii) differences in hardware and QA tools. Thus, these increasingly complex small animal treatment procedures warrant careful study and analysis from radiation physicists (Williams et al., 2010). With increasingly complex machines and treatments, comes increasingly complex quality assurance to verify dose and targeting. To maintain the integrity of the biological results, new quality assurance procedures and novel physical radiation detectors are needed to accurately verify that the intended dose has been delivered to the correct location.

Need for High Resolution Dosimetry

Microbeam radiation therapy (MRT) is a technique that differs from conventional radiation therapy in overall dose distribution, fractionation, and total dose. MRT utilizes a planar array of highly collimated, parallel x-ray beams to deliver a single high dose treatment (Anschel et al., 2011). Animal studies have demonstrated the ability for MRT techniques to use ultra-high doses to preferentially kill tumor volumes while simultaneously sparing the normal tissue (Slatkin et al., 1995; Crosbie et al., 2010). Similarly, minibeam radiation therapy (Prezado et al., 2011) utilizing beam widths of up to 700 µm has been investigated as a viable alternative to MRT, since the typical microbeam widths as needed for MRT can be as small as 20 µm (Bräuer-Krisch et al., 2003; Siegbahn et al., 2006; Martínez-Rovira and Prezado, 2011; Serduc et al., 2009) and can only be reliably produced using synchrotrons (Dilmanian et al.,

11
The MRT x-ray irradiation system developed at UNC Chapel Hill is able to produce a single collimated minibeam via the use of a carbon nano-tube (CNT) cathode (Schreiber and Chang, 2012; Chtcheprov et al., 2014; Hadsell et al., 2013; Zhang et al., 2014). This translational research irradiator, and future generation systems, seek to use minibeam radiation to attempt to reproduce microbeam radiobiological results as achieved on the much more complex and massive synchrotron facility produced MRT systems.

The dosimetry challenges surrounding all aspects of MRT cannot be overstated. Available commercial detectors are typically larger than the microbeams themselves, and are thus not capable of providing spatial resolutions as needed to characterize sub-millimeter size radiation fields. The current state of MRT dosimetry generally employs a combination of radiation detector types and/or methods (such as radiochromic film and particle transport codes) to attempt to fully characterize the dosimetric performance of a microbeam (Siegbahn, 2007). A single physical radiation detector capable of providing a real-time method of measuring the dose-rate and lateral beam profile of a microbeam would represent a significant advancement for the field.

One of the most important characteristics of a microbeam is the peak to valley dose ratio (PVDR). The PVDR is found by measuring the highest dose rate in the radiation field, and dividing this by the lowest dose rate in the spacing regions between adjacent microbeams. The PVDR has been shown to relate to both the normal tissue response and the tumor-cell killing, thus directly affecting the therapeutic ratio of the technique (Slatkin et al., 1992; Zhong et al., 2003). Historically, radiochromic film has been the best candidate for characterization of the PVDR, in addition to other parameters such as the percent depth dose (PDD) profile and scatter factors (Crosbie et al., 2008; Prezado et al., 2012; Bräuer-Krisch et al., 2009).
However, film has limitations due to the 24-hour wait time before post-processing, a complicated calibration procedure, and is sensitive to handling, making it a time consuming and cumbersome tool.

**Murine Bone Marrow Dosimetry**

Red Bone Marrow (RBM) is the primary site of hematopoietic cellular development, an essential process that continuously replenishes the body’s blood cells as are necessary for oxygen and nutrient transport, and for the defense against pathogens. Active RBM, which contains the self-renewing and multipotent hematopoietic stem cells (HSC), is located in the hollow spaces within bones, known as “trabeculae”. RBM is highly sensitive to both (i) acute radiation syndrome (ARS), and (ii) low level exposures associated with the stochastic risk of developing non-solid cancers (Leukemia). Concerning acute radiation syndrome, RBM is the primary organ at risk for absorbed doses below 4 Gy. Doses in the range of 0.25-1 Gy can lead to reduced cell counts of leukocytes, thrombocytes, and erythrocytes (Turner, 2008), but full recovery is expected. More severe doses (1-3 Gy) cause more substantial damage to the RBM, leading to increased risk of infection and sometimes resulting in death. Radioprotectants and pharmaceuticals are often tested in mouse models to attempt to minimize the damage to the BM, since BM is an essential target that should be preserved to provide radiation protection to the individual as a whole (Augustine et al., 2005).

The long term risks of radiation exposure to the BM are reflected by the high relative tissue weighting factor (see Equation C.1) assigned to it by the International Commission on Radiological Protection (ICRP). The most recent value designated by ICRP publication 103 (2007), assigned RBM the highest tissue weighting factor \( w_T = 0.12 \); equally weighted as other radiosensitive organs such as the colon, lung, stomach, and breast. The low dose thresholds necessary to produce adverse effects
for ARS and the highly sensitive radiation weighting indicative of the risk of cancer induction in the RBM make it a popular target organ for radiation biology studies.

The photoelectric effect predominates over Compton effects for photon interactions at low energy and in high-Z materials. Mineral bone has a much higher effective atomic number ($Z_{\text{eff}} = 12.61$ at 50 kV) compared to soft-tissue ($Z_{\text{eff}} = 5.64$ at 50 kV) due to the considerable amount of calcium ($Z=20, 22.5 \text{ w/o}$) present in mineral bone (Kurudirek, 2014; Woodard and White, 1986). One consequence of the photoelectric effect is the production of ionizing secondary radiation particles in the form of photo-electrons and auger electrons. As a result of the proximity of RBM to mineral bone in the trabeculae, secondary electron particles generated in bone may impart energy in the nearby RBM. The energy-range relationship of these secondaries sets up a dose gradient that varies with distance of the RBM to the mineral bone structure (King and Spiers, 1985). Concerns for the use of small animal orthovoltage energy irradiators (x-ray below 320 kV) have been raised, due to considerations of relative biological effects that may deviate from the high energy radiation sources that best model clinical radiation therapy and nuclear/radiological disasters. The study of RBM dose in mice is challenging, due to the small trabeculae of the RBM compartment, and the complex physics processes relating to the many inhomogeneities introduced by the complex mineral-bone and soft-tissue interfaces. Small animal RBM treatment procedures warrant careful study and analysis from radiation physicists, to assess these differences in relative biological effects.

1.3 Radiation Detectors

1.3.1 Overview

Ionizing radiation consists of high energy photons and charged particles, which are able to interact with atoms and nuclei. When these radiation types are of sufficiently high energy, they are able to transfer kinetic energy to atomic electrons, which leads
to the formation of electrically charged atoms, known as ions. This deposition of energy in matter, termed dose \( \frac{dE}{dm} \), is used as the unit of measurement for assessing biological damage in tissue. When living cells are exposed to ionizing radiation, through both direct and indirect mechanisms, deoxyribonucleic acid (DNA) can be damaged leading to adverse consequences, including but not limited to: cell death, mutations, and the formation of cancerous cells. Due to the health implications associated with its effects, the ability to accurately measure and quantify radiation is of paramount importance.

Radiation detectors are hardware devices that convert high energy ionizing radiation into some form of measurable signal that can serve as a surrogate way to measure the amount of energy \( dE \) that was deposited in a given mass of material \( dm \). The gold standard radiation detector for experimental measurements is generally considered to the be ion chamber. The end product of an ion chamber measurement is the charge accumulation \( nC \) in the gas volume that provides direct knowledge of the number of ionizations that occurred. Through careful calibration, the charge accumulation \( nC \) or charge current (amps) can be directly related the quantity and/or intensity of radiation that was interacting with the volume of air contained by the detector.

1.3.2 Limitations of Existing Detectors

Most modern dosimetry devices are either too large for clinical use, exhibit radiation damage under high-dose environments, or take minutes to days to obtain readings. Ion chambers may range in size from 0.1 cm\(^3\) to in excess of 1800 cm\(^3\) volume.\(^1\) Due to the physical volume of air comprising the sensitive detector, they are generally too large to be placed in-vivo. Smaller alternatives to ion chambers exist,

such as metal oxide semiconductor field effect transistors (MOSFETs) and thermo-luminescent dosimeters (TLDs). MOSFETs and TLDs can be used in the clinic to measure dose, but the readings are generally only obtained and analyzed after the full treatment has been delivered. Further, MOSFETs and TLDs are typically on the order of 2 mm in size, limiting their utility for routine implantation for measurements in brachytherapy. Optical fiber detectors are a relatively new tool that can be placed in-vivo, providing access to locations that are otherwise in-accessible to these other existing devices. Optical fiber systems provide real time signal, enabling instantaneous feedback about the treatment delivery. The development, testing, and characterization of radiation detectors of increasingly smaller size should be pursued to provide novel and unique advantages in contrast to detectors that are currently available.

### 1.3.3 Optical Fiber Radiation Detectors

There has been a recent surge in studies involving the use of scintillating optical fibers for making dose measurements, especially for use as in-vivo detectors for applications in HDR brachytherapy (Borroni et al., 2012; Andersen et al., 2009a; Cartwright et al., 2010; Moutinho et al., 2014; Suchowerska et al., 2011; Lambert et al., 2007a, 2006; Geso et al., 2004; Therriault-Proulx et al., 2013b; Tanderup et al., 2013a; Andersen et al., 2009b; Kertzscher et al., 2011, 2014a,c). Results are promising, as others have demonstrated that plastic scintillating fiber optic detectors used for $^{192}$Ir HDR treatments offered superior performance in comparison to MOSFETs, TLDs, and ion chamber detectors due to the small size (1 mm x 5 mm scintillator on a 0.98 mm core PMMA optical fiber), high accuracy (3% from 10 to 100 mm SDD), and real time capabilities (Lambert et al., 2007b). Plastic scintillating detectors have achieved 3 s temporal accuracy, 5% dose accuracy, and measurement of the radioactive source position to within 0.3 mm in water phantoms (Therriault-Proulx...
et al., 2013b). Additionally, an optical fiber system named “BrachyFOD” has been reported to exhibit less than 2% angular dependence, a distinct advantage relative to the angular performance of MOSFETs (> 10%) (Koivisto et al., 2013; Pomije et al., 2001).

Published literature on the BrachyFOD clinical plastic fiber optic detector describes a cross sectional diameter of 2.2 mm, owing to its construction using a 1 mm diameter fiber and a PVC light block coating of 0.6 mm thickness (Cartwright et al., 2010). This size has several drawbacks due to the large fiber size such as the associated large needle and catheter gauge requirements needed for in-vivo placement. Further, the scintillation element used in this detector was 4 mm in length, essentially providing a dose measurement representative of the collective radiation interactions throughout the entire volume of the scintillation element. An additional BrachyFOD detector has been described, reportedly with a core diameter of 0.5 mm. However, the stem effect signal was found to eclipse the primary scintillation signal (low SNR) when the detector was located at certain geometries with respect to the HDR source (Lambert et al., 2006). Development and clinical testing of a novel optical fiber radiation detector with reduced physical size and increased precision (smaller active volume of the scintillator) capability would represent a significant advancement for the field.
The purpose of this chapter is to describe the development, construction, and component selection of the hardware and software that make up the novel optical fiber radiation detector fabricated using a nano-crystalline scintillator material (Stanton et al., 2014). The technical performance specifications of the NanoFOD system will be explained and a brief overview of the design and assembly of the NanoFOD hardware and software components will also be given. Novel applications of this proposed optical detector required increased accuracy in the real time quantification of the light output collected via the optical fiber assembly. Through scientific discovery and iterative engineering, the first generation prototype developed by Stanton, et. al. was further improved upon, resulting in a next-generation detector system capable of performing dose measurements in environments with a wider range of radiation energy and with increased performance at low dose rates. The hardware design improvements outlined in this chapter expand on this prior work, highlighting improvements to signal to noise ratio (SNR), temporal accuracy, and ease of use in both pre-clinical and clinical settings.
2.1 Introduction

This chapter expands on previous works which describe the construction and testing of a novel optical fiber radiation detector fabricated using a nano-crystalline scintillator material (Stanton et al., 2014). The optical fiber assembly continues to be fabricated in-house at Duke, with the remaining electrical components sourced from commercial off the shelf hardware items. Hardware choice for two detector systems ((i) small animal, and (ii) human clinical radiation therapy) reflects the differences in hardware requirements based on the specific task at hand. Experiments and testing were conducted to validate the nano-crystalline scintillator based fiber optic detector (NanoFOD) system performance to (i) maximize the signal to noise ratio, (ii) minimize the overall cross sectional size of the optical fiber detector, and (iii) to allow for sampled measurements to be performed at a rate in excess of 20 Hz.

Advantages of fiber-optic detectors include: real time dose measurements, minimal artifacts in imaging or dose perturbation owing to the use of low Z components and materials, and sub millimeter diameter fiber sizes (Figure 2.1). Plastic scintillator based fiber-optic dosimeters have been widely studied for use and applications in radiation therapy measurements (Archambault et al., 2007; Beddar et al., 1992b; Beddar, 2006; Moon et al., 2012). Prior work has shown the ability of fiber-optic dosimeters, that feature 5 mm-long plastic scintillators, to measure small radiation fields down to 1 cm diameter (Letourneau et al., 1999). Similarly, fiber-optic sensors assembled in 2D arrays have been demonstrated to measure radiation field sizes down to 1.5 x 5 cm with a resolution of 5 mm (Lee et al., 2008). The NanoFOD system explained here is a similarly constructed device, that achieves higher resolution dose measurements due to the small volume of the inorganic scintillation material.

The major advantage of using the nano-crystalline phosphor material lies in the simplicity of calibration. The rest of the NanoFOD system serves the sole purpose of
measuring the optical power output from the nano-crystalline phosphor, and enabling the real time storage and display (Figure 2.2). Thus, the hardware and software was designed and assembled in a manner consistent with these goals of real time use and ease of calibration, and to preserve linearity through the entire detection chain (fiber, diode, digital multimeter (DMM), etc.).

Aside from the optical fiber and scintillation material, the remaining hardware comprising the NanoFOD system were commercial off the shelf (COTS) products.
Figure 2.2: Hardware components assembled to form the NanoFOD system. The yttrium oxide nanocrystalline scintillator material exhibited linear response under x-ray excitation (Stanton et al., 2014). Using this phosphor in the construction of a detector system required preservation of this linear behavior through the entire cascade of sub-systems (fiber, diode, data acquisition and logging, etc.).

They were integrated into a single system, and conveniently arranged on a cart allowing for the mobile transport of the system. This enabled the detector system to be rolled in and out of small animal areas, and similarly provided easy access for monitoring treatments in the clinic.

Radiation induced attenuation (RIA) occurs in optical fibers due to the generation of color centers (non-bridging oxygen hole centers) via ionization processes in the fiber material. These color centers absorb and attenuate the propagated optical signal at specific wavelength regions, characteristic of the absorptive properties of the induced color centers (Stapelbroek et al., 1979). The losses are specified in units of dB per unit fiber length. As such, increased lengths of irradiated fiber will
have more RIA due to a larger quantity of color centers generated. Time dependent kinetics of the generation and recovery govern the attenuation, such that the dose rates and time between subsequent use and exposure impact the overall magnitude of the effect (Morita and Kawakami, 1989a). The metastable component of RIA can be removed via annealing and photo-bleaching which increase the speed of recovery (Griscom, 1984); however, a permanent component of the RIA remains, and is responsible for persistent residual losses (Lu Valle et al., 2006). Plastic optical fibers (POF) with Polymethyl Methacrylate (PMMA) core material were shown to have higher RIA (<0.1 dB/10m up to 800 Gy) as compared to pure silica core fibers (<0.15 dB/10m up to 10^6 Gy) for kGy and MGy dose levels under 60Co irradiation at room temperature (Henschel, 1994). PMMA fibers are commonly used in the construction of plastic scintillator fibers as reported by others (Therriault-Proulx et al., 2013a; Beierholm et al., 2014; Protopopov and Vasil’chenko, 1995), whereas the NanoFOD fibers were constructed solely with silica fibers (Stanton et al., 2014). For low dose rate applications (< 10^4 Gy/hr), pure silica fibers have superior RIA performance compared to doped silica fibers (West, 1988). For pure silica fibers, it has been suggested that the manufacturing processes and dopants in the fiber play a more substantial role than the OH (hydroxyl bond) content in determining resistance to RIA (Friebele et al., 1985).

Published RIA studies in optical fibers often require the irradiation of tens to hundreds of meters of fiber length at kGy dose levels and at dose rates of 150+ Gy/min to produce losses on the order of ≈dB (Morita and Kawakami, 1989b; Ott, 2002). For the clinical experiments and medical applications best suited for NanoFOD use, only a 5-10 cm length of fiber is expected to be placed in the primary, high dose radiation field (1-10 Gy/min), with the remaining length of fiber located outside the primary field and/or at large distances from the radioactive source. Thus, the NanoFOD is expected to be subjected to a comparatively low dose and low dose rate.
environment, and the resultant attenuation losses due to RIA will be small as the generation of color centers will only occur in a very short length of the fiber.

2.2 Hardware Components

The basic mechanism by which the NanoFOD functions, is via the generation of optical photons that are collected and measured using a series of electronic subsystems. Each of the components will be briefly described below:

2.2.1 Scintillation Pellet

An in depth discussion of the chemistry is beyond the scope of this document, and interested readers are referred to the Ph.D. dissertation written by Ian N. Stanton (Stanton, 2013). A cursory overview of the scintillation material and manufacturing process related to its use in dosimetry will be discussed here.

The first component in the chain of systems used for the NanoFOD radiation detection system, is the scintillation element. The scintillation element is comprised of an inorganic nanocrystalline material with chemical composition of \( [Y_{1.9}O_3 : Eu_{0.1}, Li_{0.16}] \), developed and optimized (for light yield) by the Therien Laboratory at Duke University (Stanton et al., 2014). Under x-ray excitation, the photon energy is transferred to this material, generating a cascade of electron-hole pairs, that ultimately thermalize and lead to the emission of 611 nm optical photons. This scintillation process is known as radiative recombination (Lecoq et al., 2006), and primarily occurs at the europium f-block state of this material.

Construction of the usable form of the scintillation volume first started with the synthesis of a nanocrystalline powder, produced by a flame-combustion manufacturing process (Stanton et al., 2014). The powder was then pressed into a single pellet form, yielding a macroscopic wafer that was easy to work with and well suited for attachment to the terminus of an optical fiber (Figure 2.3). Resultant scintillation
Figure 2.3: Depiction of a nano-crystalline scintillator pellet attached on the end of the NanoFOD optical fiber.

Pellets, one configuration of which is shown in Figure 2.4, had an overall thickness of approximately 11 micrometers when prepared using a 1 mg/7 mm hand press (Pike Technologies, Fitchburg, WI). Depending on the intended use and application of the specific fiber, different configurations of pressed pellet quantities and material density (3 mg/7 mm press) could be created and affixed on the end of the optical fiber proving tunable volume and light output configurations. The trade-off for using more pellets was higher light output via increased optical photons consequential to the increased mass, but this came at the sacrifice of resolution since the volume of the material was also increased. The mass of material added to the hand press was tested at levels of 1 mg, 3 mg, and 6 mg. The 1 mg mass when pressed and manufactured into a fiber with one particle on the tip yielded 4 pW of light signal when following the acceptance testing procedure (See Appendix B) with the PM100USB and S150C diode system. The maximum light yield configuration was found to occur when a mass of 3 mg of material was pressed, and when a total of three particles were attached to the end of the optical fiber, achieving 35 pW of light signal; nearly an order of magnitude more signal than the first fibers that were constructed.
2.2.2 Optical Fiber

The NanoFOD is a real time detector, meaning that it has the ability to nearly instantaneously provide information about the intensity of the x-ray environment that the nano-crystalline material was exposed to. As is the case with nearly all real time detectors, a wire or some other form of a physical lead is generally required to carry the signal from the sensitive detector element to the location where signal processing, digitization, and display can occur. For MOSFETs and ion chambers, a copper electrical wire is used. For the NanoFOD, an optical fiber waveguide was used to transport the 611 nm photons to the photo diode detector. Optical fibers are well suited for this purpose owing to the: (i) ability to propagate signals over large distances with low losses, (ii) small cross sectional diameter, (iii) advantages afforded by the nature of an optical primary signal, and (iv) the use of low-Z construction.
materials making them mostly radio-opaque in x-ray imaging (Figure 2.5).

Figure 2.5: NanoFOD fiber was visible in x-ray images, with less attenuation than larger micro-MOSFETs and ion chamber detectors. This x-ray image was acquired on the Precision X-ray XRAD-225Cx small animal image guided irradiator at 80 kV with the imaging filter (2 mm Al). The aSi CsI (Tl) flat panel detector utilized 200 micron pixel size.

For the multi-mode step index pure silica core fibers used here for the construction of NanoFOD fibers, the resultant attenuation from 1 meter of fiber length was reported by the manufacturer to be \( \approx 0.01 \text{dB} \) at 611 nm wavelength for both high OH (UV/Vis) and low OH (Vis/IR) content fibers.\(^1\) This \( \approx 0.01 \text{dB/m} \) attenuation value represents attenuation of 0.23\% signal after 1 m of propagation (99.77\% transmission). Figure 2.6 shows the theoretical attenuation of 611 nm light as a function of fiber length using these manufacturer provided values. All NanoFOD fiber systems used for preclinical studies were less than 30 m in length, and the majority of the clinical fibers were \(< 2.5 \text{ m} \) in length with expected attenuation of the primary collected light signal represented in Figure 2.6b. Thus, fiber attenuation was not a substantial source of signal loss for the short fiber lengths used for the clinical

NanoFOD devices (transmission > 99%), since optical fibers are designed to minimize optical power loss to enable telecommunication and transmission applications where many kilometers of fiber length are necessary. In addition, the NanoFOD calibration process accounted for signal loss along the length of the fiber.

![Figure 2.6](image)

**Figure 2.6:** Attenuation of 600 nm light in UV/Vis optical fiber, showing high transmission of signal out to large distances.

Optical fibers are capable of coupling in series, enabling modular components to be added or removed to arbitrarily scale the transmission length of the optical signal. This is useful for applications such as in human radiation therapy (RT), where radiation scatter environments inside of the treatment room may necessitate that the primary optical signal be routed over a large distance to locate the radiation sensitive diode component behind shielding. Using a short (2.5 m) fiber with the attached phosphor and coupling it to a 30 m extension fiber (Figure 2.7), enabled the phosphor fiber to be connected/disconnected for easy handling, while allowing for the longer extension fiber to be left in place.

Preclinical NanoFOD fibers were constructed using either (i) 600 micron core diameter ultra low-OH visible/infrared (Vis/IR) transmission range fiber (Ceramoptec Industries Inc., East Longmeadow, MA) or (ii) 400 micron core diameter high-OH
Figure 2.7: An additional length of fiber was attached to the SMA-905 end of the NanoFOD device and routed to the diode. By using these extensions, the diode was able to be located outside of the radiation therapy vaults preventing scatter and stray radiation from being detected by the diode.

ultraviolet/visible (UV/Vis) transmission range fiber (LEONI Fiber Optics, Inc., Williamsburg, VA). Both fiber types had a numerical aperture (NA) of 0.22 (see Equation C.3) and were terminated with SMA-905 connectors. The Ceramoptec fibers utilized a fused-silica glass core diameter of 600 \( \mu m \), fluorine doped fused-silica glass cladding diameter of 660 \( \mu m \), a silicone buffer coating to 710 \( \mu m \) diameter, and were jacketed in Nylon to a final diameter of 860 \( \mu m \). The LEONI fibers utilized a fused-silica glass core diameter of 400 \( \mu m \), fluorine doped fused-silica glass cladding diameter of 440 \( \mu m \), acrylate buffer coating of 470 \( \mu m \), and Tefzel jacketing resulting in a total diameter of 700 \( \mu m \). The fiber OH (hydroxyl bond) content could be either high or low, since the 611 nm scintillation photons were in the visible range and similarly transmissive in both fiber types.\(^2\) Due to the epoxy used in the acrylate coating by the manufacturer, the upper operating temperature for these fibers was limited to 85°C. The fiber was a step index type that had a core refractive index of \( n = 1.458 \) at 600 nm optical wavelength. For the preclinical NanoFOD animal fibers constructed, Tefzel (ETFE) coatings were chosen as the exterior jacketing material.

\(^2\) Fiber Optic Cables: Assemblies, Connectors and Accessories: \url{http://i-fiberoptics.com/pdf/leoni_fo_cables.pdf}
to block light, and due to the stated “high-energy radiation resistance” to 1,000 kGy dose tolerance levels\(^3\).\(^4\)

600 micrometer core diameter fiber sizes were used for the clinical trial NanoFOD measurements due to the \(\approx 150\%\) improvement in sensitivity and slight (1\%) improvement in angular response as compared to the 400 \(\mu m\) fiber from experimental testing using the small animal x-ray irradiators. These improvements in device performance, came with a few minor trade-offs; larger fiber diameters increased the material cost of the fiber itself, and also required increased bend radii to limit optical power loss. While bending losses have not limited the applications of the NanoFOD to date, future applications may arise concerning in-vivo use where placement of the detector requires sharp bends, and reduced fiber sizes may need to be considered.

For the NanoFOD fibers that were designed and fabricated for the human subject clinical trials, 600 \(\mu m\) diameter core size fibers were used, without any jacketing material. These fibers had \(NA=0.22\) due to the use of a pure silica core and fluorine doped silica cladding. These fibers were selected for use in high temperature environments as needed for the construction of devices specific to the clinical trial study. These fibers offered roughly the same technical performance specifications as the previously described preclinical fibers; however, a buffer coating of polyimide was chosen to increase the range of operating temperature, enabling use from -190 to 385°C. The temperature reached by the endoscope cleaning device (Medivators Inc., Minneapolis, MN) during sterilization was not a concern (38°C), however, the medical grade shrink wrap components used on the fiber required heating to temperatures in excess


of 121°C\(^5,6\) which would have exceeded the acrylate buffer operational temperature of 85°C. Tefzel or Nylon was not needed in this application, due to the custom use of these shrink wrap materials in place of the manufacturer provided jacketing material.

**Challenges of Using Optical Fibers**

For bends of sufficiently small radii, evanescent wave energy in the cladding on the outside edge of the bend radiates out of the fiber, representing a loss of the propagated signal power. This occurs since the E&M wave modes propagating at the outside edge of the bend would need to travel at a velocity faster than the speed of light to maintain a plane wavefront (Senior, 1992). Since velocities exceeding the speed of light are forbidden, these modes in the evanescent wave cannot propagate.

The Leoni manufacturer catalog recommends the short term bending radius be greater than 100 times the jacket radius. In the case of the fibers used for the Coulter study clinical trials, this corresponds to:

\[
rb = 100 \times rf
\]

\[
= 100 \times 0.710 \text{ mm}
\]

\[
= 7.1 \text{ cm}
\]

Where \(rb\) is the minimum bend radius, and \(rf\) is the fiber radius of the outermost material.

The lead pig used to shield the photo-diode for the brachytherapy measurements had an inside diameter of 15 cm. The optical fiber terminated at a distance roughly 5 cm from the inside wall, due to the thickness of the photo-diode housing and the lead pig used to shield it.


the SMA-905 connector. Thus, during the best case scenario the optical fiber had a distance of approximately 10 cm allotted to make the 90 degree bend when the diode and fiber assembly was placed in the lead pig. This corresponds to a 10 cm bend radius, which is above the minimum bend radius (7.1 cm) calculated from Equation 2.3.

The critical bend radius for multi-mode signals is dependent on the optical fiber properties, and may be estimated by (Wolf, 1979):

\[ R_c \approx \frac{3n_1^2\lambda}{4\pi(n_1^2 - n_2^2)^{3/2}} \]  

(2.4)

Using Equation 2.4 the minimum bend radius was estimated to be approximately 0.3 mm, a value much smaller than that found using Equation 2.3. It should be noted that this critical radius represents the value at which substantial loss of optical power occurs, but that bending losses may also occur at bend radii less than this value.

2.2.3 Photo-diode

A silicon p-type and n-type junction (PN) photo-diode detector was chosen to convert the optical scintillation photons to an electrical signal, due to its superior dark noise performance, low cost, high quantum efficiency, ability to operate at room temperature, and large dynamic range. Additionally, PN silicon photo-diodes offer low light sensitivity performance advantages over silicon PIN diodes (intrinsic region) when a large frequency response was not needed and to minimize dark current (Hammamatsu, 2015). Table 2.1 compares alternative detector choices, which included photomultiplier tubes (PMT) and charge coupled devices (CCDs).

Others who have reported using plastic scintillator based fiber optic detectors most commonly coupled them to PMTs detectors (Beddar et al., 1992b; Beddar, 2006). PMTs are costly and sensitive devices, and simply exposing a PMT directly
Table 2.1: Relative comparison of photo detectors, data adapted from (Windhorst and Johansson, 1999).

<table>
<thead>
<tr>
<th></th>
<th>Photo Diode</th>
<th>PMT</th>
<th>Cooled CCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>$</td>
<td>$$$</td>
<td>$</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dynamic Range</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dark Noise</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quantum Efficiency</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

to high intensity room light can cause permanent damage. In addition, PMTs generally require a stable high voltage (1-2 kV) power supply, and small fluctuations in the stability of the supply (0.1%) can lead to large differences in the gain stability of the PMT (1%).

The S150C photo-diode (Thorlabs, Inc., Newton, NJ) used in the construction of the preclinical NanoFOD system was operated in photo-voltaic (PV) mode. The PV mode of operation generated a measurable voltage due to the photoelectrons produced in the material by incident light, with no reverse bias potential applied. The primary noise source in PV mode was Johnson noise, due to shunt resistance of the detector. Operating the diode in PV as compared to photo-conductive (reverse bias) mode led to lower overall noise.

The PDF10A diode (Thorlabs, Inc., Newton, NJ) utilized for the clinical NanoFOD system was operated in photo-conductive mode, requiring a reverse bias to be applied.

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plied to the diode. In contrast to the S150C/PM100USB setup, the PDF10A diode had additional OEM electronic circuitry to amplify the signal, which allowed the PDF10A device to achieve the stated “femtowatt” light level sensitivity. Overall, the PDF10A diode was more sensitive to electronic noise induced from nearby alternating current (AC) electrical circuits, and required grounding and shielding during its use, as explained in section 2.2.6.

Table 2.2: Technical performance specifications (manufacturer provided) of the diode hardware used for the construction of the NanoFOD systems.

<table>
<thead>
<tr>
<th>Manuf.</th>
<th>Model</th>
<th>Responsivity</th>
<th>Area</th>
<th>Gain</th>
<th>Rise Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(A/W) @ nm</td>
<td>(mm²)</td>
<td>(V/W)</td>
<td>(ms)</td>
</tr>
<tr>
<td>Thor</td>
<td>PDF10A</td>
<td>0.6 @ 960</td>
<td>1.1 x 1.1</td>
<td>0.6e12</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>PM100USB/S150C</td>
<td>0.65 @ 950</td>
<td>3.6 x 3.6</td>
<td>N/A</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

The two different photo-diodes (Table 2.2) used in the construction of the NanoFOD systems were selected for different purposes and applications. When coupled with the PM100USB (Thorlabs, Inc., Newton, NJ) laser power meter, the S150C diode enabled the assembly of a lightweight, portable, and USB powered detector system. This PM100USB and S150C combo was well suited for the small animal x-ray irradiation studies, where the low energy, high dose rate environments yielded pW light levels at the diode and led to sufficient SNR for this purpose. The manufacturer (Thorlabs, Inc., Newton, NJ) provided software for the PM100USB enabled control and data recording via the USB at rates of 10-20 Hz. The second NanoFOD system was primarily developed for the clinical studies performed in HDR brachytherapy where the overall light output was lower due to the high energy, low dose rate environment. This clinical NanoFOD system was built around the PDF10A diode, required an AC/DC power supply, and utilized separate hardware for the data acquisition system and voltage measurement. The NanoFOD system built around the PDF10A diode provided increased sensitivity and higher sample rates (kHz).
overall responsivity of the two diodes was wavelength dependent. Figure 2.8 shows the relative performance of the two diodes employed in the NanoFODD system constructions, and demonstrates the superior performance of the PDF10A hardware for detection of the 611 nm emissions from the yttrium oxide scintillator.

![Figure 2.8: Comparison of the diode responsivity for the femtowatt receiver (Thorlabs PDF10A) and the PM100USB power meter with the S150C diode adapter. These figures were created from data presented in the Thorlabs manuals for the respective hardware.](image)

2.2.4 Data Acquisition (DAQ)

*S150C Diode NanoFOD*

The S150C diode was connected to a laser power meter (PM100USB) which provided the analog to digital conversion of the voltage signal. This power meter connected via USB to a laptop computer running Thorlabs manufacturer provided software. The Thorlabs software allowed for the user to control the wavelength calibration (watts) setting, zeroing of the DC background level, sampling rate, bandwidth setting, number of samples to acquire, digital filtering settings, and many other parameters.
When using this diode and laser meter data acquisition hardware, the parameters were typically configured to use 611 nm wavelength calibration, “Low” bandwidth setting (15 Hz) to minimize noise, sampling rate of 10 or 20 Hz, and digital filtering of 150 points (3000 points corresponded to approximately 1 s of averaging). Experimental testing of this setup found the sampling rate of the PM100USB occurred at irregular intervals that deviated substantially from the software settings of 20 Hz, and more commonly occurred at a rate of 10 Hz (Figure 2.9).

![PM100USB Sampling](image)

**Figure 2.9:** Stock software provided with the Thorlabs PM100USB power meter (with S150C diode) yielded inconsistent sampling rates that varied with time. Here, the software was set to sample at a rate of 20 Hz, which only rarely occurred. Actual sampling rate was found to be closer to 10 Hz for the majority of the data-points.

*PDF10A Diode NanoFOD*

The PDF10A diode did not come with hardware from the manufacture for the measurement, storage, and display of the output raw diode signal. The PDF10A enclo-

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sure provided a BNC connector for coaxial cable output, allowing it to be connected to any data acquisition system with a BNC coax input. Three different data acquisition systems were utilized and tested with the PDF10A diode as shown in Table 2.3. These hardware data acquisition (DAQ) devices were all investigated for the purpose of (i) signal display to the user in real time and (ii) raw data storage enabling post processing and analysis of the radiation delivery.

The Agilent/Keysight Technologies Inc. (Santa Rosa, CA) 34410A digital multimeter (DMM) achieved high sampling rates (500+ Hz) at regularly spaced intervals. According to the manufacturer specifications, this device provided the most accurate and precise voltage measurements of all three of the DAQ systems tested. However, the 34410A was not used for the clinical HDR brachytherapy study since it only provided one BNC input, and was thus not scalable for the planned future multiplexed NanoFOD systems that would require multiple voltage inputs. This DMM was advantageous for bench-top testing and prototype development, since it had a built in display to show the user the real time voltage statistics, and did not require a laptop to make and store measurements.

For the clinical NanoFOD system used for HDR brachytherapy, DAQ hardware from National Instruments Corporation (Austin, TX) was used, capable of multiple channel voltage measurements. Both the USB-6210 and the USB-6218 BNC systems were USB powered and used the USB cable to transfer and store data on a laptop computer system. A custom developed software interface to these two NI DAQ systems was developed using LabView (National Instruments Corporation, Austin, TX) and will be discussed later in section 2.3.2.
Table 2.3: Technical data from manufacturer data sheets, for data acquisition hardware used to measure the PDF10A diode voltage. Sensitivity was defined in the NI manuals as the smallest change in voltage that could be detected.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Accuracy (µV)</th>
<th>Sensitivity (µV)</th>
<th>Sample Rate (kS/s)</th>
<th>Channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>NI</td>
<td>USB-6210</td>
<td>88</td>
<td>4.8</td>
<td>250</td>
<td>8</td>
</tr>
<tr>
<td>NI</td>
<td>USB-6218 BNC</td>
<td>88</td>
<td>4.8</td>
<td>250</td>
<td>16</td>
</tr>
<tr>
<td>Agilent</td>
<td>34410A</td>
<td>5</td>
<td>0.1</td>
<td>50</td>
<td>1</td>
</tr>
</tbody>
</table>

2.2.5 Miscellaneous Hardware Design Considerations

Light Block

Optical fibers collect light primarily via acceptance in the terminating end of the optical fiber, according the angle of acceptance specified by the numerical aperture (see Appendix C). Since the primary purpose of the NanoFOD fiber was to collect the light due to the scintillation of the yttrium oxide nano-crystalline phosphor, any and all other extraneous sources of light should be filtered out. Photo-diodes are “color-blind” detectors; wavelengths of incident light are not discriminated and all wavelengths may produce a measurable signal. As a result, ambient light from the room, lasers, and computer monitors could be collected in the optical fiber and produce a measurable voltage at the diode. The signal generated by the diode due to this ambient light was super-imposed over the NanoFOD scintillation signal, and in theory could be zeroed out by subtracting the DC background level due to the ambient sources when no radiation was incident on the phosphor. However, the ideal solution was to use a physical barrier to block the ambient light from entering the fiber in the first place, since the ambient light was not always DC.

A physical light barrier was used as the first means to filter out room light and any other sources of optical photons that may enter through the optical fiber aperture. Black tape and the HS-714 shrink material were both found to be viable solutions, when incorporated as a cap. Most commonly, light blocks were needed during cal-
ibration and for liquid water phantom measurements, when the fiber was in plain view to the ambient room lighting. In contrast to this, when the NanoFOD was placed in-vivo a physical light block to cover the fiber terminus was not necessary, since ambient room lighting was effectively removed in these tissue environments.

In addition to light collection through the aperture, small amounts of ambient optical signal were found to be collected along the entire length of optical fiber, via the cladding. While this source of optical signal was less substantial than the light collection at the fiber aperture, the red lasers used for alignment would generate considerable contamination if they intersected the fiber at any point when operating on the small animal x-ray irradiator systems. Thus, when measurements were performed using the NanoFOD, all lasers (red for small animals, green for human RT) were turned off prior to making radiation measurements. Non-laser produced light sources could be left on during measurement.

_Cerenkov Radiation, Generated in Optical Filter_

Cerenkov radiation may be generated when the speed of a charged particle exceeds the phase velocity of light in a dielectric (Čerenkov, 1934, 1937). The qualitative description of Cerenkov radiation, formed by Frank and Tamm (Frank and G, 1937), assumes an electron moving at constant speed in a uniform dielectric medium and describes this phenomena due to time dependent distortions in polarization induced in the dielectric medium which lead to observable coherent radiation. Symmetrical polarization of the dielectric is preserved radially to the direction of travel, but along the axis of travel a shock wave analogous to a sonic boom is setup, whereby atomic dipoles are distorted in the wake of the particle path (upstream), and the atomic dipoles downstream are experiencing little to no distortion due to time delay known as “retarded time”. Cerenkov radiation can be explained as a traveling wavefront set up due to the summation of the individual wavefronts from many small point sources.
according to Huygens’ principle, in which the traveling wavefront moves with an angle \( \theta \) given by:

\[
\cos(\theta) = \frac{1}{\beta n}
\]  

(2.5)

For plastic scintillating fiber detectors, researchers have previously studied the Cerenkov signal induced in the fiber itself (Liu et al., 2011; Beddar et al., 1992b; De Boer et al., 1993). The “stem effect” was a term first used to refer to the signal generated in the electrical cables and insulator materials used for the construction of ion chambers (Ibbott et al., 1975; Adams, 1962; Fowler and Farmer, 1956)), but has now been adopted to explain the signals generated in the optical cable of scintillating fibers. “Stem effects” are a linear superposition of both the Cerenkov signal and any additional fluorescence generated in the fiber apart from the scintillation material (Therriault-Proulx et al., 2013a). Due to the dependence on the refractive index of the material (Equation 2.5), PMMA fibers and silica fibers have different energy thresholds and angles of emitted Cerenkov radiation (Veronese et al., 2013). Many methods have been reported for correcting for or filtering the Cerenkov spectrum when using plastic scintillating fibers (Arnfield et al., 1996). One such method uses spectral analysis to integrate a narrow range wavelengths, so that only the scintillation emissions are considered in the analysis (Darafsheh et al., 2015). Other methods include the use of a parallel or twisted blank fiber subtraction method which requires two signals to provide the correction (Letourneau et al., 1999; Jang et al., 2011; Liu et al., 2011, 2013). Cerenkov signal induction in optical fibers has been characterized for electron beams (Beddar et al., 1992a; Yoo et al., 2013), proton beams (Jang et al., 2012), photon beams (Jang et al., 2013a), and even thermal neutrons (Jang et al., 2013b). The Cerenkov production threshold was calculated to be 191 keV for electrons traversing pure silica fibers, but other sources of fluorescence can also be
seen in these fibers at energies below this range (De Boer et al., 1993).

In general, the relative energy per unit path per unit wavelength of the Cerenkov spectrum is proportional to $\lambda^{-3}$ (Jelley, 1958). Others have calculated the intensity of Cerenkov radiation captured in an optical fiber, and found it to be inversely related to the square of the wavelength, given by (Law et al., 2007):

$$I_{cap} = N_P \frac{2\pi (2r_f)^3}{\sin \gamma} \frac{e^2}{4\pi^2 \epsilon_0 \lambda^2 c^2} \left( 1 - \frac{c^2}{n_{co}^2 \nu^2} \right) \times \cos^{-1} \left( \frac{\nu(n_{co} - \Delta n) - c \cos \gamma}{\sin \gamma \sqrt{\nu^2 n_{co}^2 - c^2}} \right) \quad (2.6)$$

With $2r_f$ being the diameter of the fiber, $N_P$ the number of charged particles, $\gamma$ the angle of the charged particle track in the direction of the detector relative to the fiber axis, $e$ the charge of the electron, and $\Delta n$ the difference of the core and cladding refractive index. Based on Equation 2.6, recommendations on how to minimize Cerenkov signal collected by an optical fiber are to use small diameter fiber (due to the cube relationship), low $\Delta n$ materials, and to orient the fiber axis approximately perpendicular with the charged particle radiation direction (Law et al., 2006).

Since the Cerenkov emissions are more intense in the UV/blue range and spectrally separated from the 611 nm emission (orange) from the NanoFOD scintillator, an optical band pass filter can be used to remove the majority of the optical power below a given cutoff wavelength. The NanoFOD system employed a 590 nm long pass optical filter made of colored glass to filter optical signal before reaching the PDF10A photo-diode (Figure 2.10).

**Lead Shielding of Diode**

The photo-diode detectors employed for the conversion of optical photons to an electrical voltage or current were also found to be sensitive to radiation. From trial and error experiments, measurable signal was shown to be generated by the PM100USB
Figure 2.10: Optical filters (550 nm long pass shown here) were placed between the sensitive detector element of the PDF10A diode and the SMA-905 connector of the fiber. Since the nano-crystalline phosphor emissions were 611 nm, and given that Cerenkov signal was peaked in the UV/blue range, the spectral separation allowed for a long pass optical filter to transmit primary signal while selectively removing the Cerenkov light.

and S150C photo-diode assembly when these diodes were located in the $^{192}$Ir treatment suite even with no fiber attached. Further tests were performed to characterize the signal level generated by the S150C diode itself, when exposed to a 6 MeV electron beam produced by a medical linear accelerator. When compared to the level generated by the NanoFOD phosphor emissions under the same radiation environment, the diode irradiated signal level was found to be 15,000 times larger. During the irradiation of the NanoFOD phosphor, no Cerenkov filtering was performed (PM100USB and S150C diode system do not allow use of optical glass filters) and the photo-diode itself was located in the vault of the linear accelerator behind 4 mm of lead shielding. Thus, the direct comparison of the diode sensitivity relative to
the phosphor NanoFOD system was likely larger than a factor of 15,000 for electron beam irradiation.

Figure 2.11 displays the overall layout of the test equipment that was used for the pre-clinical NanoFOD studies for $^{192}$Ir HDR brachytherapy. The lead shielding utilized for these experiments re-appropriated a radioactive source transport container that was already available in the clinic. This container, known as a lead “pig”, provided 4.7 cm of lead for a full 360 degrees. After placing the diode in to the lead pig from the top, two lead bricks could then be placed on top of the well to provide 5.1 cm of lead shielding to attenuate stray radiation from the top. These two bricks were positioned to leave a small space between them, allowing the electrical cables and optical fiber connected to the diode to exit the lead pig, without compromise to the shielding. By placing the photo-diode inside this lead pig, the $^{192}$Ir gammas were theoretically attenuated by $\approx 15$ half value layers (HVLs; 1 HVL = 3 mm Pb (Baltas et al., 2006)) due to the 4.7 cm of lead thickness.

_Fiber Coatings_

The outermost protective coating on an optical fiber, referred to as the “jacket”, serves to protect the fiber from mechanical damage such as scratches and cleaving, while also preventing ambient light from entering the fiber. This section will discuss the different types of coatings that were explored for use in the NanoFOD, according to the (i) biological compatibility, (ii) mechanical durability, (iii) optical opacity, (iv) radiation resistance, and (v) ease of manufacture.

For small animal studies, the fiber jacketing most commonly used was either ethylene tetrafluoroethylene (ETFE, known as Tefzel®) or nylon (polyamide) plastic. A single length of fiber was purchased with SMA-905 connectors on both ends, and cleaved in the middle to yield two devices capable of receiving phosphor tips. Since

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14 Dupont trademark name
Figure 2.11: Hardware setup for an in-scatter measurement using a vaginal cylinder applicator with $^{192}$Ir high dose rate (HDR) treatment setup. The diode was placed in the lead pig to shield it from scatter radiation in the room.

the small animal experiments were carried out on sacrificed mice, an Institutional Animal Care and Use Committee (IACUC) protocol was not needed to meet animal handling requirements or safety. Similarly, a US Food and Drug Administration (FDA) approved medical grade polymer was not required for these animal applications. Due to its ease of application and opaqueness to ambient room light, liquid electrical tape was used to coat the phosphor tip of the optical fiber. Liquid electrical tape was applied by brushing on multiple coatings to achieve the desired thickness, and each coat was allowed to cure at room temperature. Using these liquid electrical tape coatings, a factor of nearly 100 reduction in room light (Table 2.4) collected via the fiber tip was achieved, compared to a bare fiber. The electrical tape coatings were applied first using white, and secondly using a black tape color, as shown in
Figure 2.12: Construction of the fibers for small animal use was performed using liquid electrical tape to coat the tip of the fiber to prevent room light from reaching the diode. (a) Shows the Nylon jacketed NanoFOD fiber without any coatings on the tip, (b) shows the tip of the fiber after the application of the white liquid electrical tape coating, (c,d) show the finalized NanoFOD with one coat of white and one coat of black liquid electrical tape.

Figure 2.12. In theory, the white coating first used would reflect scintillator emissions back into the aperture of the optical fiber for increased sensitivity (similar technique to the aluminum reflectors used in plastic scintillators (Beddar, 2006)); and the black coating used on the exterior would absorb ambient room light, and prevent it from entering the fiber via the aperture.

Table 2.4: Testing the ability of liquid electrical tape coating to block room light collected by the tip of the optical fiber.

<table>
<thead>
<tr>
<th>Coating</th>
<th>Gross Signal (W)</th>
<th>Background (W)</th>
<th>Net Signal (W)</th>
<th>Reduction Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.38E-07</td>
<td>-4.95E-09</td>
<td>1.43E-07</td>
<td>1.0</td>
</tr>
<tr>
<td>White</td>
<td>2.81E-08</td>
<td>-2.07E-09</td>
<td>3.01E-08</td>
<td>4.7</td>
</tr>
<tr>
<td>White + Black</td>
<td>1.36E-09</td>
<td>-1.39E-10</td>
<td>1.50E-09</td>
<td>95.4</td>
</tr>
</tbody>
</table>

For the NanoFOD fibers that were used in the human subject HDR brachytherapy clinical trial studies, the use of medical grade polymers was essential for jacketing
the optical fibers, as required for approval by the Institutional Review Board (IRB). The majority of the clinical fibers were jacketed using a proprietary material fabricated from a radiation cross-linked acrylated olefin known as HS-714 (Insultab, Woburn, MA). HS-714 provided a 2:1 shrink ratio (initial ID = 2.38 mm), met biocompatibility requirements (USP Class VI), was radiation and chemical resistant, and had a quoted operational temperature range covering the environments experienced in the clinical and sanitation processes \((-55^\circ \text{C} \text{ to } 121^\circ \text{C})\).\(^{15}\) For reasons explained later (Section 3.3.5), an additional shrink wrap material was used for the tip of the NanoFOD fiber to achieve a smaller overall cross-sectional diameter than was possible with the HS-714.

The second coating used on the tip of the NanoFOD (Figure 2.13) was a polyethylene terephthalate (PET) resin polymer (Vention, Advanced Polymers, Salem, NH) medical grade shrink wrap coating. This material was selected due to the reduced wall thickness and overall diameter (initial inside diameter (ID) = 0.89 mm). PET shrink tubing offered an order of magnitude thinner wall diameter (0.025 mm) compared to the HS-714 (0.51 mm), and an order of magnitude increased strength compared to all other shrink materials.\(^{16}\) This Vention material also met various biocompatibility requirements (USP Class VI) and the data-sheet stated it could be sterilized via gamma and electron beam suggesting high durability to radiation exposure.\(^{17}\)

Use of this thin walled PET material on the distal end of the NanoFOD fiber enabled in-vivo placement of the phosphor via the use of needles and catheters. Aside from a 25 cm length at the distal end, the remaining length of the fiber was coated

---

\(^{15}\) HS-714 Data-sheet, Insultab: [http://www.insultab.com/hs714.pdf](http://www.insultab.com/hs714.pdf)


in the HS-714 shrink wrap due its superior ability to filter ambient room light and due to its superior mechanical durability and protection offered.

Figure 2.13: NanoFOD optical fiber assembly constructed using two different medical grade heat shrink components. The diameter was less than 0.9 mm at the distal end of the fiber, reduced from the original prototype diameter of 2.7 mm when the HS-714 shrink wrap was used for the entire fiber.

2.2.6 System Integration Testing

Grounding

The PDF10A clinical NanoFOD system utilized the following electrical components for the assembly of the entire detection system:

- Laptop Computer
• Photo-diode and power supply
• NI DAQ board
• Tripp-Lite rack mount power strip, with 15A circuit breaker

All four of the above components were assembled to share a common electrical ground via the attachment to either a (i) solid copper block fixed on the cart (Figure 2.14a) or (ii) connection provided by the Tripp-Lite power strip. Short lengths of 6 AWG (~2.1 mm) diameter copper stranded wire were used for grounding, to limit the inductance and maintain a low resistance path to ground. Further, a grounded alligator clip connector was attached to the SMA-905 connector of the PDF10A photo-diode for all measurements; by grounding this hardware component a 60 Hz noise signal was found to be reduced by roughly −28 dBV (Figure 2.14b). The noise was most likely induced in the sensitive diode component by the alternating current (AC) voltage from the power supply connected to the wall outlet.

2.3 Software

The NanoFOD has been previously described as a “real-time radiation dosimeter” (Belley et al., 2015). To provide “real-time” dose output, electronics and custom software were assembled and developed to convert the raw signal readings (voltage or joules) to dose rate.

2.3.1 Data Analysis and Post-Processing - Python

Software was developed using Python\textsuperscript{18} and various numerical and plotting toolkits such as Numpy (Van Der Walt et al., 2011), Matplotlib (Hunter, 2007), SciPy (Jones et al., 2015), and Pandas (McKinney, 2010) to efficiently manipulate the raw data. The purpose of the software was to automate the data analysis as much as possible.
and to quickly provide signal statistics (min, max, average, standard deviation, cumulative integral) to the user. The data analysis was broken up into several steps, as shown in Figures 2.15 and 2.16, for the PM100USB/S150C and the PDF10A diode NanoFOD systems, respectively. Overall, the final output of the program was a figure that displayed the data representing the delivered radiation, with the x-axis displaying time and the y-axis displaying dose rate. Software samples can be found in Appendix A.

Two separate programs were developed for post-processing the raw data, one for each diode detector system. The signal to noise level was sufficiently large when using the PM100USB/S150C system for small animal measurements, and allowed for the development and implementation of an algorithm that automatically detected the
Figure 2.15: Flow chart of the software developed in Python, enabled automatic processing of batches of output files when using the PM100USB and S150C diode system. The cumulative light output for the regions displayed by yellow, was $8.317 \times 10^{-11}$ J.

“beam on” time. Therefore, the final version of this software could automatically calculate the background signal and provide a final dose value for each irradiation (Figure 2.15) with limited interaction needed from the user. Further, a “batch import” function was developed, allowing for a single fiber calibration dataset to be applied to a wide range of raw data files, speeding the analysis considerably when processing large datasets.
In contrast, the software developed for the PDF10A diode data was aimed at processing the clinical HDR brachytherapy datasets where lower SNR values were more common. The resulting software designed for processing the PDF10A diode data files provided an interactive graphical user interface (GUI) to the user, which enabled the user to selectively analyze the data. Thus, the user highlighted regions of the data that corresponded to background and regions which corresponded to signal, where the cumulative dose was to be calculated (Figure 2.16). For the clinical treatments utilizing the PDF10A diode system, this method of analysis was found to be more robust (due to false positives) than the automatic signal detection algorithm that was developed for the PM100USB/S150C NanoFOD system.

**Figure 2.16:** Flow chart of software developed in Python, enabled data to be reduced and displayed to the user for interactive analysis of the dataset from the PDF10A diode. Final dose was 656.8 cGy for this treatment, representing the cumulative value for the region highlighted in red.
2.3.2 *LabView Data Acquisition for PDF10A Diode System*

A LabView software tool was created to control the data acquisition for the PDF10A diode NanoFOD system, when using both the NI USB-6218 BNC and the USB-6210 DAQ boards. The software allowed the user to set the sampling rate, number of samples to acquire, and to give the file name and location where the data was desired to be stored. The real time voltage data was displayed during signal acquisition as shown in Figure 2.17. This software was developed to be easily scalable to the maximum number of inputs afforded from the NI DAQ hardware. In practice, the real time voltage signal displayed to the user could be changed to provide a calibrated real time dose rate display to the user.

![Screen-shot of the LabView program front-end GUI](image)

**Figure 2.17:** Screen-shot of the LabView program front-end GUI for the clinical NanoFOD software that was developed to acquire and display real-time signal from a treatment. The treatment displayed here, shows an actual clinical patient measurement from a tandem and ovoid treatment with two needles (Vienna applicator). Data was acquired at 50 Hz.
The purpose of this chapter is describe the development of the NanoFOD system for brachytherapy radiation therapy dosimetry measurements. This chapter lays out the mathematical formalism used to calculate dose, methods of calibration developed and tested, methods and results from phantom measurements conducted for evaluating device accuracy, and an overview of the clinical trials conducted using this detector for gynecological brachytherapy. Energy dependence, dose-rate dependence, and dose accuracy were all characterized.

3.1 Introduction

Error detection sensitivity and specificity with in-vivo brachytherapy detectors is not easily achieved, since placement with accurate positional knowledge is required for comparison to the treatment planning software (TPS), and is challenging due to possible movement of organs and the applicator. Past studies with alternative in-vivo dosimeters have compared detector response to the TPS planned dose, and discrepancies have been reported to be greater than 20% for measurements of dose to OARs (Nose et al., 2008), 9% for urethral dose during prostrate treatments (Su-
chowerska et al., 2011), and greater than 40% when measuring rectal dose during prostate HDR (Seymour et al., 2011). Most commonly, these large differences were attributed to positioning uncertainty, and difficulty of localizing the detector position. Treatments such as these in which the dosimeter data was compared to the planned or expected dose data based on a-priori knowledge of the detector position, are known as static error detection algorithms (Kertzscher et al., 2014b). More recently, researchers have developed “adaptive error detection algorithms” to attempt to suppress the false positive rate of detected errors due to uncertainties in the reconstruction of the detector position by way of the static error detection algorithm method, thus removing the need for a-priori knowledge of the detector position prior to treatment (Kertzscher et al., 2014b).

3.1.1 Dose Equation and Mathematical Formalism

One commonly used isotope for HDR brachytherapy is $^{192}\text{Ir}$ ($T_{1/2} = 73.91\ d$). $^{192}\text{Ir}$ decays by $\beta^{-}$ (95%) and electron capture (EC), emits a range of gamma energy emissions [0.061, 1.378] MeV, has an average gamma energy of 0.37 MeV, and has an overall effective energy of 0.398 MeV (Baltas et al., 2006). $^{192}\text{Ir}$ is produced in nuclear reactors and is first encapsulated in a titanium or stainless steel vessel, and later laser welded to the end of a guide wire before it can be used in a remote afterloader. The beta particles have limited range, and can thus be absorbed by the encapsulating vessel such that the primary radiation responsible for treatment delivery are the gamma rays.

Brachytherapy dosimetry requires personalized treatment plans adapted to patient specific contoured CT/MR fused image data-sets. This 3D treatment planning approach allows for conformal dose plans to be delivered using up to date information about patient anatomy. The treatment planning systems used at Duke calculate the dose based on validated computer models of dose distributions to liquid water,
using formalized procedural dose calculations as explained in AAPM TG-43 (Rivard et al., 2004; Nath et al., 1995).

TG-43 is a dosimetry protocol prepared by a task group of the American Association of Physicists in Medicine, which defines water \((\rho = 0.998 \text{ g/cm}^3, 22^\circ)\) as the medium in which all dose is calculated. It assumes full scatter conditions and no inter-source attenuation effects. The dose profile to water from a cylindrical radiation source is defined from TG-43 according to:

\[
\hat{D}(r, \theta) = S_K \cdot \Lambda \cdot \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} \cdot g_L(r) \cdot F(r, \theta) 
\]  

(3.1)

Where \(\hat{D}(r, \theta)\) is the 2D dose-rate distribution, \(S_K\) is the air kerma strength with units of cGy cm\(^2\) h\(^{-1}\), \(\Lambda\) is the dose rate constant with units of cGy h\(^{-1}\) U\(^{-1}\) (1 U = \(\mu\)Gy m\(^2\) h\(^{-1}\)), \(g_L(r)\) is the radial dose function (line source approximation), \(G_L(r, \theta)\) is the geometry function (line source approximation), and \(F(r, \theta)\) is the 2D anisotropy function. The geometry function takes into account the near inverse-square fall off behavior from a line source. The reference points are defined as \(r_0 = 1 \text{ cm}\) and \(\theta_0 = 90^\circ\). Due the difficulty of making physical measurements due to the steep dose gradients associated with brachytherapy, typically \(g_L(r)\) and \(F(r, \theta)\) are found using Monte Carlo particle transport codes to generate tables of values for specific source geometries.

TPS dose calculations to water using TG-43 have been shown by others to provide a good approximation for calculating dose in \(^{192}\text{Ir}\) gynecological brachytherapy procedures; since for this application the dose calculation is not sensitive to tissue and geometrical differences in attenuation and scattering, as the radiation source is at a deep-seated position in the body (Rivard et al., 2009). Further, soft tissue has only minor differences (<1%) in calculated anisotropy \((g(r))\) compared to water for \(^{192}\text{Ir}\) dosimetry within 10 cm distance of the source (Melhus and Rivard, 2006),
indicating that doses calculated to water translate well to values expected in soft tissue.

With the exception of brachytherapy, most physical dosimetry measurements in radiation therapy are performed to measure the dose to water in water via an ionization chamber. Ion chambers are calibrated at an AAPM accredited dosimetry calibration lab (ADCL), and are used to very accurately calculate dose after applying several correction factors according to:

\[
D_w = N_w \cdot M \cdot k_p \cdot k_T \cdot k_p \cdot K_{ion} \cdot k_V \cdot k_{appl} \cdot k_{m,w} \cdot k_{wp}
\]  

(3.2)

Where \(D_w\) is the dose to water, \(N_w\) is the chamber calibration factor (usually for \(^{60}\)Co reference beam), \(M\) is the detector measurement, \(k_T\) is the temperature correction factor, \(k_p\) is the pressure correction, \(k_{ion}\) adjusts for ion recombination, \(k_V\) corrects for the finite volume of the ion chamber, \(k_{appl}\) corrects for attenuation effects due to the catheter and applicator materials, \(k_{m,w}\) adjusts for the perturbation effects of the detector in the medium relative to when that volume is filled with liquid water, and \(k_{wp}\) corrects from liquid water to the phantom material. However, for brachytherapy dosimetry, ion chambers are not ideal dosimeters due to the large physical size of the active volume which averages the dose measurement over a finite volume, making the dose measurement meaningless in the steep dose gradient regions close to the source. For HDR brachytherapy, dosimeters should have high sensitivity (response per unit dose) and a small active volume so that (i) they do not perturb the radiation field they were introduced to measure, and (ii) to limit dose volume-averaging effects within the gradients (Baltas et al., 2006).

The goal of this work was to develop and test the NanoFOD for making dosimetry measurements in HDR brachytherapy. As a starting point, the NanoFOD was used to calculate dose in water using a simplified dose equation similar to Equation 3.2 used for ion chambers, and with some additional modifications as needed. Thus, the
first step was to develop a dose calculation formalism for the NanoFOD.

3.1.2 Energy Dependence for $^{192}$Ir

As the distance increases between the $^{192}$Ir source and detector (source detector distance (SDD)), the scatter-to-primary ratio of radiation changes, shifting the overall average of the beam to a lower effective energy (Figure 3.1). In addition, the proportion of dose contribution due to the primary and scattered radiation components changes with SDD, and at 6 cm SDD the dose contributed by all scatter exceeds the dose from the primary radiation (Taylor and Rogers, 2008). This change in radiation energy as a function of SDD poses a major challenge when calibrating radiation detectors that are not “water equivalent”, since materials with atomic numbers that differ from those of water will have different rates of photoelectric absorption leading to differences in absorbed dose that change non-linearly with energy. These aforementioned effects consequential to non-water equivalent detectors are commonly referred to as “energy dependence”. Specifically for the NanoFOD, the $Y_2O_3$ ($Z$-effective = 39) material used for the scintillation element was not water equivalent ($Z$-effective = 7.4) and exhibited substantial changes in light output that were dependent on the absorbed radiation energy (Stanton et al., 2014). Concerning HDR brachytherapy, light output was sensitive to the location of the detector relative to the $^{192}$Ir source. Due to this energy dependence, a single calibration point was insufficient when the intention was to use the NanoFOD at variable source detector distances, as was the most desirable use for NanoFOD. This chapter will highlight characterization of the light output changes of the NanoFOD for various SDDs in $^{192}$Ir HDR brachytherapy use.

Existing literature showed that energy dependence was not unique to the NanoFOD. When used for HDR brachytherapy, semiconductor based radiation detectors, such as silicon diodes, exhibited sensitivity changes that amounted to differences of 75%
depending on placement and SDD (Williamson et al., 1993). For silicon diodes, it has been demonstrated that this energy dependence can be corrected for by applying appropriate correction factors to account for radiation energy changes (Kirov et al., 1995). Therefore, a goal of this chapter was to seek correction factors and methods of utilizing the NanoFOD in a manner that allowed it to accurately calculate dose for various SDD positions.

Thermo-luminescent dosimeters (TLDs) are commonly recommended for use as the best “fully developed” medium for dosimetry (Perez-Calatayud et al., 2012), mainly due to the small active volume size and only minor variation in energy dependence relative to water for photon energies above 80 keV (Muench et al., 1991). Disputed claims of observed energy correction factors of up to 8.5% within the range of 1-10 cm (Meigooni et al., 1988) have more recently been replaced by data that support calibration at a single SDD value and subsequent TLD use at any SDD
(within 15 cm) without the need to apply a correction factor. In support of this claim, one study showed less than 3% variation in TLD response comparing 15 cm to 1 cm SDD positioning (Karaiskos et al., 1998), and another study showed a 2.5% variation in TLD response comparing 10 cm to 1 cm SDD (Pradhan and Quast, 2000). Due to this lack of energy dependence, TLDs (Z-effective = 8.4) were used as the “gold standard” comparison for the NanoFOD vaginal cylinder brachytherapy clinical trial study. It should be noted that for the highest accuracy measurements, TLDs are recommended for dosimetry at distances greater than 3 cm SDD and have been shown to produce systematic error of approximately 10% when used within 2 cm SDD (Kirov et al., 1995).

TLDs exhibit linear responses up to 100 cGy (for \(^{60}\)Co), after which the response is supra-linear (Baltas et al., 2006). This is in contrast the NanoFOD performance which has not shown any loss of linearity across the tested ranges of dose-rates and cumulative doses for orthovoltage x-ray irradiation (Stanton et al., 2014). This chapter reports investigations performed to test if the NanoFOD had a saturation limit for use in \(^{192}\)Ir HDR brachytherapy.

*Silver Cap*

Photon beam diodes incorporate a radiation shielding material around the sensitive detector element, to preferentially absorb low energy photons that would otherwise cause over-response due to the non-water equivalence of the silicon material acting as the sensitive volume in the diode (Eklund and Ahnesjö, 2010, 2009; McKerracher and Thwaites, 2006). With the shield, the silicon material in the diode will primarily “see” the high energy un-attenuated radiation that is more likely to penetrate the shield. Commonly, a high-Z material such as tungsten is chosen, due to the advantageous high mass-attenuation coefficient for low energy photons attributed to its k-edge photoelectric absorption probability (Figure 3.2). When used in large radiation fields,
photon field diode energy dependence has been found to be significantly reduced (less than 1%), via the use of a shielding material such as tungsten (Sauer and Wilbert, 2007). For small photon fields (less than 25 mm circular), un-shielded diodes were shown to provide more accurate dose results than shielded diodes due to the reduction in scatter (McKerracher and Thwaites, 1999).

Figure 3.2: Attenuation coefficients for water, silver, and tungsten in the energy range relevant to $^{192}$Ir. Deviation of the upper curves relative to that of water demonstrates that for low energy photons, the k-edge photoelectric absorption probability dominates in the high-Z materials. Figure was generated in XMuDat, using material data published by Boone (Boone and Chavez, 1996).

In this chapter, the testing, design, and development of a silver “cap” material was explored for use with the NanoFOD system. The use of the cap aimed to achieve a similar energy dependence correction effect as tungsten shielding on silicon diodes. Silver ($Z = 47$) was chosen for the shielding material due to its high atomic number, and ease of machinability, since tungsten posed several challenges due its poor machinability and associated difficulty to create small hardware parts.
3.1.3 Cerenkov Radiation and the “Stem Effect”

Cerenkov radiation physics as relevant to optical fiber detectors was previously introduced and discussed (Section 2.2.5). This chapter will focus on discussing the application of the Cerenkov filter design and its effects on the measured signal specific to the application of dosimetry in brachytherapy. The ultimate goal was to obtain optical signal measurements at the diode that were independent of the “stem” effects.

3.1.4 Calibration

The calibration of the NanoFOD involved the development and testing of a means to convert the measured light output to a dose-to-water value at the location of the phosphor. Ideally, calibration should allow for the NanoFOD phosphor to be located within any reasonable distance from the $^{192}$Ir source, and for an accurate dose or dose-rate value to be obtained. The recommendations by Baltas (Baltas et al., 2006) were carefully considered throughout all stages of calibration: scattering media in the room should not be within 1 m of the test setup, a full 24 cm of water is needed to fully saturate scatter conditions as needed for TG-43, ion chambers should use the build-up cap when making measurements to remove the contamination of electrons, and that PMMA and acrylic are equally valid construction materials for phantoms (Meli et al., 1988).

Due to the near point-source geometry, accurate positioning of the NanoFOD relative to the source (SDD) was essential to minimize the resulting uncertainty in the calibration. The high dose gradients encountered for HDR brachytherapy mean that a 1 mm shift in position at an SDD of 5 cm can amount to an error of 4% in the measured dose (Baltas et al., 2006).
3.1.5 Phantom Accuracy

Phantom studies offered a valuable means to test the NanoFOD accuracy prior to making measurements in patients. Phantoms provide a known “truth” for geometry, thus simplifying the treatment setup testing by limiting variables, and allowing for a quick way to perform repeat measurements at later dates. This is in contrast to patients, in which anatomical variations and changes in applicator geometry can lead to both inter-fraction (day-to-day) and also intra-fraction changes. Phantom studies for $^{192}$Ir most commonly used liquid water to conform to objects submerged in it, and since water was the medium which TG-43 formalism was based.

3.1.6 Clinical Trials

This chapter discusses the results of a NanoFOD optical fiber developed with a cross sectional diameter of < 0.9 mm, to monitor dose via adjacently placed brachytherapy catheters. An observational clinical trial was designed to test prospective clinical feasibility for gynecologic high dose rate brachytherapy implants.

The NanoFOD was considered to be a non-significant risk device, when categorized according to the definitions given by an FDA guidance document.\(^1\) The NanoFOD was therefore under an abbreviated IDE as per 21 CFR Part 812.2(b). A non-significant risk rating was arrived at due to (i) no additional surgery or procedures were necessary that could lead to potential harm of the patient, (ii) the device itself did not present a serious health risk to the patient, (iii) the device was not a permanent implant, (iv) the device was not used to support or sustain human life, and (v) the device was not impacting the standard of care via a diagnosis, cure, or treatment of the disease.

The study objectives were twofold: (i) to measure dosimetric accuracy of the

NanoFOD by direct comparison to the treatment planning software (TPS) dose, and
(ii) to determine feasibility for use via the subjective opinion of the physician and
overall device impact on the clinical work flow and usability.

Vaginal Cylinder Applicators

The first patient cohort of the clinical trial approved under the IRB protocol name
of “Real time in-vivo dosimetry for gynecologic brachytherapy” sought to measure
the dose for simple (vaginal cylinder applicator) treatments with an accrual goal of
30 measurements.

Tandem and Ovoid/Ring Applicators

The second patient cohort of the clinical trial approved under the IRB protocol name
of “Real time in-vivo dosimetry for gynecologic brachytherapy” sought to measure
the dose for complex (tandem and ovoid/ring applicator) treatments with an accrual
goal of 30 measurements.

3.2 Methods and Materials

The methods and materials discussed here will include a description of the radiation
detection system (a.k.a NanoFOD), calibration equipment and hardware that was
designed and fabricated, and the clinical tools and equipment needed for the patient
measurements.

3.2.1 Energy Dependence for $^{192}\text{Ir}$

The energy dependence was characterized via the calibration of the NanoFOD at
various SDD values and by direct comparison of the measured signal to the calcu-
lated dose rate at the location of the phosphor. For more details on the calibration
methods, see section 3.2.3.
**Silver Cap**

Use of the machined cap was pursued as a possible means of mitigation of energy dependence. To attempt to prevent any additional detrimental effects to angular response that would result from uneven thickness, tight tolerance constraints were placed on the hardware design specifications for the cap. The original cap was designed to use tungsten shielding material, but due to limitations of the machinability of the tungsten hardware part with this specified wall thickness (0.2 mm), a cap made of silver was ultimately pursued. The engineering drawing of the tungsten hardware and finalized machined part are shown in Figure 3.3. Larger thicknesses were not pursued, since larger cross sectional diameter devices would limit access for in-vivo use. Calibration data was acquired using the cylinder calibration method with the silver cap placed over the tip of the fiber.

![Figure 3.3](image-url)

**Figure 3.3:** (a) Conceptual design of the tungsten cap hardware (not shown to scale) with wall thickness of 0.2 mm. Machine shops contacted were unable to fabricate this hardware using tungsten ($Z=74$), so the actual hardware piece (b) was fabricated using silver; a more easily machinable element, also with a relatively high $Z$ number ($Z=47$).
3.2.2 Cerenkov Radiation and the “Stem Effect”

Figure 3.4: Calibration of the first generation (2.7 mm diameter) NanoFOD device was performed by using Tegaderm Film (3M, Saint Paul, MN) to attach the NanoFOD to the side of the vaginal cylinder applicator (a). The applicator was then submerged in a water bath (b), to simulate the scatter and radiation environment encountered in a patient and according to TG-43 dosimetry protocol formalism, which calculates dose to water.

An optical glass filter was implemented (as explained in Section 2.2.5) to absorb wavelengths of light below 590 nm, preventing them from reaching the photo-diode while still permitting the 611 nm scintillator emissions to be transmitted. Measurements were performed both pre- and post-filter implementation to characterize the effect of the filter on the Cerenkov signal transmission for HDR brachytherapy use. The intended outcome after implementation of the filter was to achieve NanoFOD signal levels that varied in relation to the dose at the location of the NanoFOD phosphor. Experiments were performed using the geometry shown in Figure 3.4, and with the goal of acquiring the expected signal depicted in Figure 3.5.
3.2.3 Calibration

*Free In Air vs. Ion Chamber*

Preliminary studies with the NanoFOD sought to establish calibration values for $^{192}$Ir irradiation free in air and to test if the detector system response was linear with decreasing dose rates. The goal was to acquire three measurements at distances of 3, 5, and 10 cm. According to the physics of a point source geometry, the exposure from the $^{192}$Ir source should approximately obey the inverse square law with increasing SDD values. The setup used to test this hypothesis is shown in Figure 3.6. The HDR afterloader used at Duke was the GammaMedplus iX (Varian Medical Systems, Palo Alto, CA), which utilized an active pellet of $^{192}$Ir with a length of 3.50 mm and a diameter of 0.70 mm (Perez-Calatayud et al., 2012).
Figure 3.6: Experimental setup for the earliest $^{192}$Ir HDR NanoFOD studies performed, in which the fiber was connected to the PM100USB/S150C diode. No Cerenkov filtering was used and the diode was not shielded for these studies.

**Cylinder Calibration**

The first method of calibrating the NanoFOD for use in vaginal brachytherapy applications was developed using similar geometry to the clinical treatment plans. The NanoFOD optical fiber was attached to the side of a vaginal cylinder phantom applicator (Figure 3.4A), and the entire assembly was submerged in liquid water to simulate the radiation scatter environment relevant to both TG-43 and the actual treatment (Figure 3.4B). Next, a treatment plan utilizing 10 s (nominal time for a 10 Ci source) source dwells for the entire length of the applicator was delivered. The NanoFOD signal was acquired with individual visualized voltage values for the discrete dwell positions of the Ir source. Using CT images of the location of the detector (Figure 3.7B) allowed the individual dose rates to be determined at the location.
of the phosphor using the TPS. Finally, the calibration data was calculated as a function of SDD by combining these aforementioned TPS (dose rate) and NanoFOD (voltage) values for each individual source dwell position (Figure 3.7C).

Figure 3.7: (a) Calibration setup of the second generation miniaturized NanoFOD (0.9 mm diameter) attached to a 3 cm diameter cylinder and immersed in water. (b) CT image used to derive dose rate values in the treatment planning software (TPS). (c) Cylinder method calibration curve of the NanoFOD system. The $^{192}$Ir source (8.258 Ci) was stepped through 10 s (10 Ci planned) dwells along the length of the cylinder applicator.

A mathematical formalism for using the NanoFOD to calculate absorbed dose to water was developed, based on the assumption that the entire medium was made up of homogeneous liquid water, with no bone or air. These cylinder based NanoFOD calibration experiments calculated dose based upon ‘n’ discrete dwell positions of the $^{192}$Ir source, according to:

$$D_w = \sum_{i=1}^{i=n} \left( N_{D,w}^{E_{\text{ref}}} k_Q \right)_i \times (G_i - B) \times t_i$$  \hspace{1cm} (3.3)

Where $t_i$ was the dwell time of the ‘$i^{th}$’ dwell position, $G$ was the gross NanoFOD signal level (V), $B$ was the NanoFOD background signal level (V), and $(N_{D,w}^{E_{\text{ref}}} k_Q)_i$ was the quality corrected dose conversion factor ($cGy/V \cdot s$) as shown in Figure 3.7C. By
using this cylinder calibration method, \((N_{D,w}^{E_{ref}} k_Q)_i\) values were experimentally measured based on each of the discrete dwell positions of the source. When the NanoFOD was later used for dose measurements in a treatment with different geometry than the calibration, the SDDs encountered were at intermediate values compared to the discrete points measured. In cases such as these, \((N_{D,w}^{E_{ref}} k_Q)_i\) specific to the treatment were found from interpolation of the cylinder calibration data using a non-linear regression fit. Measured values of \((N_{D,w}^{E_{ref}} k_Q)_i\) performed using an alternate calibration geometry (not cylinder measurements) are shown in Table 3.1.

Table 3.1: Trends of experimental calibration values in comparison to the approximate relationship of the f-factor ratio of the nano-crystalline yttrium oxide material relative to liquid water. F-factors were computed using mass attenuation data (Boone and Chavez, 1996) at the root mean square (RMS) energy at each SDD value, and the \([N_{D,w}^{E_{ref}} k_Q]_i\) value was measured experimentally for \(^{192}\text{Ir}\) using a NanoFOD optical fiber positioned in liquid water. The reference energy for calibration was defined at 3 cm SDD.

<table>
<thead>
<tr>
<th>SDD (cm)</th>
<th>(f_{\text{water}}^\text{nano})</th>
<th>([f_{\text{water}}^\text{nano}]<em>{E-\text{ref}} / [f</em>{\text{water}}^\text{nano}]_E)</th>
<th>([N_{D,w}^{E_{ref}} k_Q]_i) (cGy V(^{-1}) s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>23.1</td>
<td>1.00</td>
<td>21.66</td>
</tr>
<tr>
<td>5</td>
<td>32.0</td>
<td>0.72</td>
<td>15.74</td>
</tr>
<tr>
<td>7</td>
<td>40.9</td>
<td>0.56</td>
<td>10.61</td>
</tr>
<tr>
<td>9</td>
<td>45.2</td>
<td>0.51</td>
<td>9.63</td>
</tr>
</tbody>
</table>

The TG-43 dosimetry protocol has been shown to underestimate the dose rate from \(^{192}\text{Ir}\) HDR treatments in water beyond radial distances of 10 cm (Lambert et al., 2007b). SDD values beyond 10 cm required the use of Monte Carlo tabulated dose rate tables. For a vaginal cylinder treatment with a 3 cm stump and 3 cm length template the maximum source-detector-distance encountered when using the NanoFOD was only 3.1 cm. Thus, the TG-43 dosimetry protocol could be used to calculate the dose for calibration purposes of the NanoFOD for vaginal cylinder applications. However, for treatments that involved larger source detector distances such as tandem and ovoids (12 cm) and tandem and ring, the calibration should be
Fixture Calibration

A second, novel method of calibration was developed to account for energy dependence when using non-water equivalent scintillation materials during $^{192}\text{Ir}$ high dose rate (HDR) brachytherapy radiation therapy (RT). This calibration method allowed for the conversion of the radiation detector signal to a real time dose rate value. Development, testing, and implementation has focused on providing both (i) real time dose rate data and (ii) post-treatment cumulative dose data from a single sensor detector system specific to the treatment of gynecologic tumors using fixed geometry with a dose applicator. Conceivably this calibration method can be expanded to other areas of radiation detection and measurement, and the calibration procedure is directly scalable for calibration of multi-detector systems.

In effect, the NanoFOD calibration was performed according to Equation 3.4 based on formalism similar to the AAPM TG-51 report for ion chamber dose-to-water calibration, given by:

$$\dot{D}(x) = N_{D,w}^{E_{\text{ref}}} \times k_Q(E) \times V$$  

(3.4)

Where $N_{D,w}^{E_{\text{ref}}}$ is the light output to dose conversion value at a reference beam condition ($cGy/V \cdot s$), $k_Q(E)$ is the beam quality correction factor, and $V$ is the net voltage measured by the NanoFOD system at any given instant in time.

The treatment site for gynecological radiation therapy is to a soft tissue target volume. Due to the photoelectric interaction probability behavior exhibiting nearly a cubic relationship with the effective atomic number of the material as a function of the photon energy, a non-linear absorbed dose relationship manifests in which the absorbed dose to the yttrium oxide scintillation material far eclipses that of water and soft tissue for low energy photons. Thus, for materials exhibiting energy dependence
$k_Q(E) \neq 1$, whereas if the medium were water equivalent $k_Q(E) = k_Q \approx 1$. Herein lies the challenge for calibration of inorganic scintillation materials that exhibit energy dependence.

For $^{192}$Ir, the radiation energy changes with SDD due to attenuation of the primary radiation and the production of both (i) secondary radiation and (ii) lower energy scatter. Practically speaking, this means that a different calibration value is needed for each SDD value at which the detector is used at, to account for the respective radiation energy at that location. In water, a relationship of the radiation energy vs SDD can be obtained, yielding a reformulation of Equation 3.4:

$$
\hat{D}(x) = N_{D,w}^{E_{ref}} \times k_Q(x) \times V
$$

Equation 3.5 shows how the NanoFOD was first calibrated and used for HDR brachytherapy measurements due to its similarity with the cylinder calibration equation (Equation 3.3). As is apparent, knowledge of the SDD value ($x$) is necessary to calculate dose using Equation 3.5. A new calibration equation was used that did not require user input for the SDD value ($x$). This discovery is predicated on the facts that (i) for $^{192}$Ir, the clinical source activity was well known at the time of use (source activity is calibrated in units of Curies) and (ii) due to the relatively long half life ($\approx 74$ days), the activity did not change appreciably during the time span of a single clinical measurement (5-10 min). Further, it has been previously demonstrated that the NanoFOD response was directly proportional to the source activity. Thus, Equation 3.5 can be re-formulated so that the beam quality correction value can be determined according to the real time voltage ($V$) value based on knowledge of the source activity ($a_s$):

$$
\hat{D}(x) = N_{D,w}^{E_{ref}} \times k_Q(V, a_s) \times V
$$

70
The beam quality correction value was based solely on the instantaneous voltage measurement (V), and the activity of the radiation source \( a_s \). Thus, real time dosimetry could be performed with the NanoFOD, as enabled by performing calibration according to Equation 3.6.

Equation 3.6 dictates that the relationship for \( k_Q(V, a_s) \) should be found to have a working calibration for the NanoFOD (assuming \( N_{E_{ref}}^{D_{ref}} \) has been previously measured). The relationship of \( k_Q \) can be further simplified based on findings from past experiments that have demonstrated linearity for the NanoFOD response relative to the source activity. This finding allowed the light output from the NanoFOD to be scaled directly by the activity value. The clinical tradition of using a 10 Ci nominal source strength provides \( k_Q(V, a_s) = k_Q \left( \frac{V \times 10 \text{ Ci}}{a_s} \right) \), which is found to solve the relationship of \( k_Q \) for the general case of all source activities. It should be noted that this formulation of \( k_Q \) in Equation 3.6 is based on the assumption that one and only one voltage can correspond to a given SDD value. This one-to-one (monotonic) relationship is necessary, since a given voltage (V) should uniquely correspond to only a single beam quality correction value.

A calibration jig was designed, validated, and implemented for the use of NanoFOD calibration (Figure 3.8). This jig allowed for up to five NanoFOD optical fibers to be located at radial distances of 3, 5, 7, and 9 cm from the \( ^{192} \text{Ir} \) source for direct measurement of voltage (V) as a function of SDD (x).

The jig was submerged completely in liquid water to simulate the scatter and radiation environment as would be encountered during routine clinical measurements in-vivo. A single NanoFOD optical fiber response curve was obtained by taking voltage measurements at the four distinct distances of 3, 5, 7, and 9 cm and by fitting an equation of the form \( y = a \cdot x^b \) to the data.

Combining the equation found from the NanoFOD relationship (SDD vs. voltage
Figure 3.8: (a) Drawing and tolerances used for the design of the calibration jig hardware, (b) rendered 3D visualization of the calibration jig concept, and (c) assembled calibration jig hardware submerged in a water tank for calibration measurements of NanoFOD alongside an ion chamber. This water tank met the recommendation of Baltas (Baltas et al., 2006) to use 24 cm of water to generate full scatter conditions necessary to accurately replicate dose reconstruction using the TG-43 dosimetry protocol.
Table 3.2: Phantom dose template used to test accuracy of the 10 s cylinder dwell calibration method.

<table>
<thead>
<tr>
<th>Dwell (cm)</th>
<th>10 Ci Nominal Dwell Time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130.0</td>
<td>31.8</td>
</tr>
<tr>
<td>129.5</td>
<td>40.4</td>
</tr>
<tr>
<td>129.0</td>
<td>34.1</td>
</tr>
<tr>
<td>128.5</td>
<td>17.6</td>
</tr>
<tr>
<td>128.0</td>
<td>3.2</td>
</tr>
<tr>
<td>127.5</td>
<td>3.7</td>
</tr>
<tr>
<td>127.0</td>
<td>19.2</td>
</tr>
<tr>
<td>126.5</td>
<td>40.5</td>
</tr>
<tr>
<td>126.0</td>
<td>56.3</td>
</tr>
</tbody>
</table>

at a known activity) with dose data from tabulated TG-43 tables (dose vs. SDD), one could then fully represent the relationship of \( k_Q \left( \frac{V \times 10 \text{ Ci}}{a_s} \right) \). Moreover, \( k_Q \) could now be used to calculate the dose from a given voltage measurement, using Equation 3.6. The result, was an empirical formula for \( k_Q \) relating the NanoFOD light output response to dose, relative to a 10 Ci nominal source strength.

3.2.4 Phantom Accuracy

After calibration was completed using the cylinder calibration method (10 s dwells, with NanoFOD attached to cylinder) a phantom dose treatment was delivered according to a clinical dose template utilizing a 3 cm stump, 4 cm length template, and with a target dose of 5 Gy to 0.5 cm depth in tissue. The source activity was 8.258 Ci, and the dwell times used for this treatment template are shown in Table 3.2.

To test the repeatability of the measurement, two treatments were delivered using the phantom setup. The first phantom measurement was performed with the NanoFOD left in place at the same location as the 10 s dwell calibration. For the second phantom measurement, the Tegaderm Film (3M, Saint Paul, MN) was removed, and the NanoFOD was reattached with a new Tegaderm Film at the 11 cm
distance from the base of the 3 cm diameter cylinder to test the effects of variation in positioning due to the operators ability to accurately re-position the detector, as expected to occur during inter-fraction setup.

3.2.5 Clinical Trials

Clinical trial measurements were performed to test the accuracy of the fixture calibration method. In theory, the NanoFOD was capable of providing near “real time” measurements, since no user input was necessary to provide SDD or $k_Q$ values according to Equation 3.6. However, for the clinical trial, “real time” processing was not performed since no added benefit would have been achieved since the data was not allowed to be used to guide the treatment in any way. Raw data was collected, and software was used to later automatically reduce the data and calculate the cumulative dose from the treatment procedure. These clinical trial measurements were essential for validating the NanoFOD performance for various treatment geometries.

Vaginal Cylinder Measurements

Treatment plans followed the Duke standard of care. The treatment plans varied case by case, but utilized vaginal cylinders typically in the range of 3-3.5 cm diameter, with dose length templates ranging from 3-4 cm, and with target doses of either 4 or 5 Gy. A sample treatment plan used for one of the clinical NanoFOD measurements is shown in Figure 3.9.

Similar to the cylinder calibration setup described above, the NanoFOD was positioned at a known location (either 11 or 12 cm depending on the treatment) from the base of the cylinder, and fixed in place using sterile Tegaderm (Figure 3.10). This Tegaderm film served two purposes: (i) to fix the geometry so that the location of the detector could not shift between the imaging and treatment phases, and (ii) acting as the first physical barrier between the patient and the NanoFOD device.
Figure 3.9: Treatment plan used for the first clinical NanoFOD measurement in the first patient treated on the study. The dose template was planned to deliver 4 Gy to 0.5 cm depth, using a 4 cm length template and a 3 cm diameter stump.

At the same distance from the base (11 or 12 cm) two TLD-100 LiF chips were attached to the cylinder using the same method with Tegaderm. The TLDs are labeled in the results section as “TLD1” and “TLD2”. Locating the TLDs in this manner maintained radially symmetric detector placement, so that the TLDs were exposed to approximately the same dose levels as the NanoFOD. After all detectors were attached, the cylinder was covered by a sterile transducer cover (second physical barrier) and the cylinder apparatus was placed in the vaginal vault according to the standard of care.

After placement of the applicator, cone beam (CBCT) images were acquired using the Acuity System (Varian). Images were reconstructed with 1 mm slice thickness to provide the highest resolution images possible for localization of the NanoFOD and TLD positions. Later, these images were used to reconstruct the dose using the TPS (Figure 3.11), separately from the standard of care planning performed per
Figure 3.10: NanoFOD and TLDs were attached with radial symmetry to a location that corresponded to roughly the central dwell channel of the $^{192}$Ir source. The $^{192}$Ir source stepped through the dwells in increments of 5 mm steps, leading to changes in the source-detector-distance with time due to the fixed geometry of the NanoFOD and TLD. Thus, real time signal tracings of the NanoFOD displayed a discrete step function relative to time, with a maximum signal when the SDD value was a minimum.

After CBCT images were acquired of the applicator within the patient, the Varian HDR afterloader was connected to the source guide. The NanoFOD optical fiber was connected to the photo-diode, and the photo-diode was placed in the lead pig within the room for shielding purposes. Next, the NanoFOD data collection was started, and all physicians, nurses, and investigators left the brachytherapy treatment room.
Figure 3.11: Eclipse TPS interface showing the CBCT images of the patient with the cylinder applicator positioned in the vaginal vault. The dose template has been added to the images, allowing for the visualization of the isodose lines and the calculation of the TPS dose measurement at the locations of the TLDs and NanoFOD system.

Once outside the treatment room, the plan was delivered according to the normal standard of care. Post treatment, the NanoFOD data acquisition was stopped, the TLDs and NanoFOD device were disassembled from the cylinder applicator, and the fiber was then sent back to be sanitized in a Medivator and repackaged for the next treatment (Figure 3.12A). TLDs were stored in darkness until the entire TLD batch had been irradiated, after which they were sent back to the University of Wisconsin ADCL for a third-party measurement of the dose delivery.

Part way through the trial (starting on fraction 9 of 30), a new method of locating the NanoFOD optical fiber was implemented. For this new configuration, a Flexi Needle (Best Medical International, Inc., Springfield, Virginia) with a blunted tip was attached directly to the cylinder instead of attaching the NanoFOD (Figure 3.13). Using this setup, the CBCT imaging was performed with only the Flexi Needle in
Figure 3.12: (a) The first clinical NanoFOD device, after sanitation, and ready for use in the first patient. Post treatment, a CT image was acquired of the NanoFOD optical fiber attached to the side of the cylinder during calibration in a water bath. A sizable air pocket was visible in the CT images (b), created due to the over-sized shrink wrap used as the physical barrier in the first generation NanoFOD.

place, and then the NanoFOD was placed in the Flexi Needle immediately prior to treatment. The Flexi Needle provided enhanced contrast in the CBCT images since it could be visualized due to the hollow air cavity it created within the patient. The NanoFOD was fed into the Flexi Needle prior to treatment, but after CBCT imaging, providing an easy and reliable means of quickly placing the detector. This application, of placing the NanoFOD down clinical catheters and needles, was made possible due to the hardware design and engineering improvements which resulted in the reduced cross sectional diameter in comparison to the first generation device.

The equipment setup was photographed immediately following a cylinder patient treatment, as shown in Figure 3.14. The cart was positioned next to the lead pig, and beside the patient table. The location of the equipment as depicted represents the relative location of the equipment during treatment, allowing the clinical team sufficient room to move around the patient and the treatment table.
Figure 3.13: Preparation of the vaginal cylinder applicator showing fixation of the Flexi Needle via Tegaderm, to locate the tip of the fiber at 12 cm distance from the base.

Figure 3.14: The NanoFOD system on the mobile cart unit, inside of the HDR treatment room. The cylinder and NanoFOD assembly is shown, with the diode inside of the shielded lead pig. The computer display shows the data from a cylinder patient measurement that was just completed.
3.3 Results and Discussion

3.3.1 Energy Dependence for $^{192}$Ir

Via the direct calibration of the NanoFOD, data showed substantial changes in the calibration value ($[N_{D,i}^{E_{ref}} k_Q]_i$) as a function of the SDD (Table 3.1). Going from 3 cm to 9 cm SDD, the measured voltage (and thus the scintillator light output) increased by a factor of 2.25 per unit dose to water (TG-43 based). This change in NanoFOD light output sensitivity (2.25) was in agreement with the change in the $f$-factor of the yttrium oxide scintillation material relative to water (1.96). These $f$-factors were calculated as the ratio of the scintillator value relative to water for the RMS energy at 3 cm and 9 cm SDD (Table 3.1). These findings suggest that the increased light output was consequential to the high-Z materials (Yttrium) used in the scintillator construction.

3.3.2 Cerenkov Radiation and the “Stem Effect”

*Discovery via Preliminary Experiments*

Preliminary experiments found significant deviations in the collected NanoFOD data from the expected inverse square fall-off of the radiation signal for a free-in-air measurement (Table 3.3). In seeking to determine root cause for the order of magnitude higher signal measured by the NanoFOD compared to the inverse-square expected value, root cause was theorized to be (i) signal generated by radiation interactions in the photo-diode itself and (ii) Cerenkov radiation. Further experiments were carried out to test these hypotheses, and both (i) and (ii) were identified as root cause.

One test found that by increasing the distance of the PM100USB/S150C photo diode detector from the source, the measured voltage was reduced by a factor of two. This finding confirmed that the photo-diode itself was radiation sensitive even without an optical fiber and scintillation material attached. Corrective action was im-
plemented for all subsequent experiments performed after this finding by placing the photo-diode in a lead shielded container (discussed in Section 2.2.5), and experiments were again performed to show that no signal was generated by the photo-diode itself when shielded. Shielding was also verified by the good agreement of the NanoFOD signal compared to an ion chamber (Model: TN30006. PTW, Freiburg, Germany) for a free-in-air measurement (Figure 3.21).

Table 3.3: Prior to implementing the diode shielding and Cerenkov filtering, additional and undesirable signal was noticed in the photo-diode measured optical power from the irradiation of the NanoFOD phosphor at three distances. The “Expected ISQ” data column shows values calculated from theory, according to the inverse square exposure rate in air for a point source using the 3 cm SDD value as the reference.

<table>
<thead>
<tr>
<th>Distance (cm)</th>
<th>Power (W)</th>
<th>Expected ISQ (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.08e-10</td>
<td>2.08e-10</td>
</tr>
<tr>
<td>5</td>
<td>2.06e-10</td>
<td>7.50e-11</td>
</tr>
<tr>
<td>10</td>
<td>1.81e-10</td>
<td>1.88e-11</td>
</tr>
</tbody>
</table>

The Cerenkov radiation hypothesis was confirmed via an in-phantom measurement with a vaginal cylinder applicator. The NanoFOD was attached to the side of the cylinder similar to the cylinder calibration method (Figure 3.10), and the $^{192}$Ir source was stepped through all dwell positions for 10 s at each location. The resulting voltage signal (Figure 3.15) increased to a maximum value at the minimum SDD, but as the source then moved past the fiber tip and along the proximal side of the fiber at the base of the cylinder the signal was not found to decrease as expected. Thus, root cause was identified to be Cerenkov radiation via the close distance of the $^{192}$Ir source to the NanoFOD “stem”. For the 600 micron core diameter silica fiber attached to a 3.5 cm diameter vaginal cylinder and submerged in liquid water, the maximum Cerenkov signal generated by the fiber was approximately 40 mV for a source strength of 5.577 Ci.
Figure 3.15: Acquired NanoFOD signal after shielding the diode, prior to implementing the Cerenkov filter. 3.5 cm diameter cylinder applicator was used, with setup and geometry as shown in Figure 3.4. The signal was expected to be symmetric, with maximum voltage achieved at the minimum source detector distance (SDD) as the source translated along the central axis of the cylinder. Collected data deviated from the expected signal and signal generation via the fiber itself was observed, suggesting that Cerenkov may be contributing to the measured signal. Three different filtering techniques were investigated for smoothing the raw data, as shown here.

Cerenkov Removal Results

The method of Cerenkov removal determined to be the best course of corrective action was the use an optical band-pass filter to remove all wavelengths of light below the 611 nm emission of the scintillator. Due to the $\lambda^{-3}$ intensity behavior of the Cerenkov light, the band pass filter was found to adequately remove a substantial amount of the Cerenkov optical power to achieve sufficient signal-to-noise measurements to obtain the accurate and expected signal as shown in Figure 3.16B.
Figure 3.16: Data before (a) and after (b) implementing the optical Cerenkov filter. Signal was acquired using 10 s dwells spaced at 5 mm along the central axis of a vaginal cylinder applicator. Note, changes in signal level between (a) and (b) were due to many factors, such as the use of a different NanoFOD fiber and differences in $^{192}$Ir source activity on the day of each experiment. After implementing the Cerenkov filter, (b) data showed good agreement to the expected signal, depicted in Figure 3.5.

Silver Cap

According to preliminary Monte Carlo experiments, increasing the material thickness was shown to achieve better energy dependence correction by preferentially filtering more of the low energy scatter, but at the cost of reduced device sensitivity since the primary radiation was also shielded (Figure 3.17). Thus, a wall thickness for the shielded cap was optimized using Monte Carlo analysis, and selected to be 0.2 mm of tungsten material which yielded a 12% change in RMS energy comparing 2 cm to a 6 cm SDD, while maintaining a sensitivity of 39% compared to the unshielded case. The unshielded NanoFOD Monte Carlo results showed a 26% change in RMS energy over the same range of distance, indicating a factor of two reduction in the relative energy change via the use of the shielded cap. Ultimately, a 0.2 mm wall
thickness silver cap was fabricated, with Monte Carlo results suggesting that the 2 cm to 6 cm SDD RMS energy change would be 20% for this material, and the sensitivity would be reduced to 69% relative to an unshielded NanoFOD. The raw data showing agreement to the TPS dose behavior is displayed in Figure 3.18.

![Figure 3.17](image)

**Figure 3.17**: Monte Carlo analysis results, looking at the root mean square (RMS) detected energy inside of a given shielded cap thickness of specified material. The tungsten (W) material was found to be a superior material compared to silver (Ag) for the same thickness of material.

According to Monte Carlo simulations performed, the 0.2 mm silver cap that was machined had an equivalent effect as 0.05-0.1 mm of tungsten. Similarly, the thickness of silver needed to achieve the same effect as 0.2 mm of tungsten, was in the range of 0.5-1.0 mm of silver, depending on which metric was sought for equivalence (mean E, RMS E, or sensitivity). The sensitivity ratio predicted from simulation for 0.2 mm silver was 0.691, versus the measured value of 0.672; a deviation of only 2.7% that demonstrated good agreement between the Monte Carlo and the experimentally measured data.

When tested using the calibration fixture, the silver cap shielded NanoFOD displayed a substantial reduction in the energy dependence. The silver cap data showed
Figure 3.18: Calibration setup (a) with the tip of the NanoFOD placed at 11 cm distance from the base of the cylinder. The NanoFOD named C6 used the 0.2 mm thick silver cap on a 2.3 cm diameter vaginal cylinder applicator. Calibration data (b) showed good overlap of TPS measured dose (10 Ci, 10 s planned dwells) relative to the NanoFOD signal voltage. TPS marker was shifted 2 mm, since visualizing the location of the phosphor was impossible due to the high-Z metal artifact in the CT images caused by the silver.

only a 59% change in the calibration value over the range of 3-9 cm SDD, whereas the unshielded NanoFOD had a change of 125% (Figure 3.19). Additionally, the silver cap was shown to mitigate energy dependence for distances greater than 5 cm, as evidenced by the nearly zero slope value of the calibration curve at distances of 5 cm and greater. An ideal response for a water equivalent detector with no energy dependence would be zero slope for all distances, indicating 1:1 correlation between
light output and dose, and thus independence of radiation energy and SDD.

**Figure 3.19**: Calibration performed using the silver cap on fiber “C6” using the acrylic test fixture designed to provide in water measurements at 3, 5, 7, and 9 cm SDD. With the silver cap, the absolute calibration factor increased by more than 60%, indicating less overall light was generated in the phosphor per unit dose as was measured by an ion chamber (Model: TN30006. PTW, Freiburg, Germany). The uncertainty in the calibration values was highest at the 3 cm location, due to uncertainties in positioning; small errors in \( dr \) at small SDD lead to the largest errors due to the steep dose gradients close to the source. Uncertainties were estimated using Table 7.3 in Baltas (Baltas et al., 2006), which states that at \( r=5 \) cm, an uncertainty of 0.5 mm in radial positioning can lead to an uncertainty of 2.00% dose.

Overall, simulation and experimental results found that the PROS of using the silver cap were:

- Cap blocked 100% of ambient room light from being collected by the tip of the optical fiber.

- Reduced overall energy dependence from 125% to 59% at 9 cm SDD relative to 3 cm.
• Data suggests possible use of a single calibration value may be viable when using NanoFOD at SDD values greater than 5 cm.

The CONS of using the silver cap were found to be:

• Sensitivity reduced by 33% using 0.2 mm of silver shielding material.

• Fiber diameter increased from 0.9 mm to 1.4 mm with addition of the silver cap.

• High Z artifacts introduced when imaging the silver cap for x-ray CT.

3.3.3 Calibration

10 s Dwell Cylinder Calibration

The cylinder calibration values were acquired by direct comparison of the NanoFOD voltage at each SDD value in comparison to the TG-43 TPS dose rate. The calibration data (Figure 3.20) was fit with an exponential curve (R² >0.99), providing calibrated light output to dose rate values in the range of 1.5-4 cm SDD.

Fixture Calibration

An in air measurement was first performed using the acrylic calibration fixture to test accuracy of the NanoFOD placement, and for direct comparison to the ion chamber (Model: TN30006. PTW, Freiburg, Germany). Plotting the raw in air value of the NanoFOD voltage compared to the raw ion chamber data resulted in a highly linear trend (R² >0.999), suggesting accurate positioning of the 3, 5, 7, and 9 cm distances on the calibration fixture and good linearity of the NanoFOD system for increasing dose rates (Figure 3.21).

Further, additional ion chamber measurements were made when the acrylic calibration fixture was submerged in liquid water and were directly compared against
Figure 3.20: Calibration data and trend line fit of the NanoFOD “C6” fiber using the cylinder calibration method (source steps of 5 mm using 10 s nominal dwells). Calibration data was obtained via comparison of the NanoFOD voltage to TPS dose values at each SDD.

TG-43 along/away data (Perez-Calatayud et al., 2012), as shown in Table 3.4. Temperature and pressure corrections applied to the ion chamber measurements are shown in Appendix C.3. Uncertainties of less than about 5% indicate good agreement, considering no volumetric corrections were applied to account for the volume averaging effects of the ion chamber. In contrast to this, the NanoFOD raw data plotted in comparison to the ion chamber data showed substantial energy dependence, manifested as the over-response of the NanoFOD raw voltage signal with increasing SDD (Figure 3.22).

The calibration data for the two clinical NanoFOD fibers (voltage relative to the SDD in liquid water) acquired using the calibration fixture are shown in Figure 3.23. A power fit ($R^2 > 0.999$) was applied to the data points for interpolation at intermediate SDD values. For the fiber named “C10”, the coefficient of variation (COV) in the fit values of $a$ and $b$ were 2.45% and 1.13%, respectively. Likewise, for fiber “C11” the COV values were 6.78% and 2.85% for the coefficients of $a$ and $b$, respectively.
Figure 3.21: The calibration jig was first validated by comparing measurements of the ion chamber to the NanoFOD, using a free-in-air geometry setup. The relationship between these two sets of measurements was highly linear ($R^2 = 0.9998$) indicating that the manufacturing tolerances used provided accurate positioning of the NanoFOD relative to the ion chamber. Measurements were acquired at 3, 5, 7, and 9 cm SDD.

Table 3.4: Comparison of relative ion chamber measurements from the fixture calibration method as compared to relative TG-43 along/away values. The 9 cm TG-43 value was extrapolated from the dataset in the range of 3-7 cm, since the dose tables only provided values out to a maximum of 7 cm “away”.

<table>
<thead>
<tr>
<th>SDD (cm)</th>
<th>Ion Chamber (a.u.)</th>
<th>TG-43 (a.u)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.000</td>
<td>1.000</td>
<td>0.0%</td>
</tr>
<tr>
<td>5</td>
<td>0.366</td>
<td>0.358</td>
<td>2.2%</td>
</tr>
<tr>
<td>7</td>
<td>0.189</td>
<td>0.180</td>
<td>5.2%</td>
</tr>
<tr>
<td>9</td>
<td>0.112</td>
<td>0.109</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
Figure 3.22: Over-response of the raw NanoFOD voltage relative to the ion chamber measurements for increasing SDD, demonstrated the energy response of the NanoFOD in liquid water. “C10” and “C11” were the names of the two clinical NanoFOD fibers.

The dose rate data as needed for calibration was adapted from Table XVII in the AAPM/ESTRO report #229 (Perez-Calatayud et al., 2012) which provided along (z) and away (y) dose rate data specific to the Varian GammaMedPlus source. The data tables only went out to a distance of 7 cm away (y), so the data was extrapolated out further to obtain an estimate of the 9 cm away value for use with the 9 cm SDD calibration distance on the acrylic test fixture. Lastly, a power fit curve of the form $y = a \cdot x^b$ was applied to the dose-rate-to-water vs SDD data (Figure 3.24).

Figure 3.23 and 3.24 were fitted using the scaled Levenberg-Marquardt algorithm for multivariate optimization. In contrast, fitting power trend lines using Microsoft Excel yielded slightly different fits. Microsoft Excel first transformed the equation of $y = a \cdot x^b$ to the linear form of $\ln(y) = \ln(a) + b \cdot \ln(x)$ and then solved the latter using a linear regression model. The Excel generated trend-lines were $y =$
Figure 3.23: Recorded net voltage of clinical fibers named “C10” and “C11” as a function of distance, acquired using the calibration test fixture for $^{192}$Ir. Voltage was scaled to represent signal from a 10 Ci nominal source strength.

The equations $y = 0.853 \cdot x^{-0.709}$ and $y = 0.664 \cdot x^{-0.777}$ were determined for the “C10” and “C11” NanoFOD fibers (same format as Figure 3.23), respectively. Similarly, the TG-43 trend-line (same format as Figure 3.24) solved for using Excel was found to be $y = 13.24 \cdot x^{-2.024}$. Comparing the regression values of Excel and the Levenberg-Marquardt algorithm, the difference in $a$ and $b$ was $-2.39\%$ and $0.90\%$ for fiber “C11”, and $2.10\%$ and $-1.13\%$ for fiber “C10”. Similarly, the difference for the TG-43 coefficients of $a$ and $b$ for these two regression models were $1.06\%$ and $0.20\%$, respectively. All clinical data was analyzed using the regression values from Microsoft Excel. The final calculated cumulative dose difference for clinical patient measurements was less than 3\% between the Excel derived and the Levenberg-Marquardt derived calibration equations, a value within
3.24: TG-43 based dose rates to water for radial distances from the source matching the corresponding SDD values at which the NanoFOD was calibrated at using the calibration fixture. Scaled values (extrapolated out to 9 cm) were adapted from Table XVII in AAPM/ESTRO report #229 (Perez-Calatayud et al., 2012). Absolute doses were obtained by scaling the 3 cm data point to the absolute dose rate value taken from Eclipse clinical TPS at 3 cm SDD.

a similar range as the uncertainties in the calculated coefficients.

3.3.4 Phantom Accuracy

1.5% agreement (717.0 cGy NanoFOD, 706.4 TPS TG-43 dose) was observed comparing the NanoFOD to the TPS for the first phantom measurement and 3.1% agreement (731.8 cGy NanoFOD, 710.1 TPS TG-43 dose) for the second trial when the NanoFOD was removed from the cylinder and re-attached. The dose calculations performed using the cylinder calibration method were not “real time” since user input was required to provide knowledge of the SDD value (and thus $k_Q$) of each individual dwell position as required for dose calculations using Equation 3.3. The
measured total treatment time of the first NanoFOD phantom measurement was 299.5 s compared to the TPS planned time of 298.9 s. For the second treatment the NanoFOD measured treatment time was 299.3 s compared to the TPS planned time of 298.9 s. Good agreement among the NanoFOD real time data and the TPS values suggest accurate temporal accuracy of the NanoFOD signal.

3.3.5 Clinical Trials

Vaginal Cylinder Applicators

The first patient measurement was acquired using the first generation optical fiber jacketed in the HS-714 shrink wrap. Due to the diameter of the HS-714, a small air pocket at the tip of the fiber was noticed in the CT images as shown in Figure 3.25. This air pocket introduced large uncertainty in localizing the position of the fiber (and thus the sensitive phosphor), making it difficult to obtain a dose value from the TPS. Uncertainty in the range of a few mm at this position translated to differences in TPS calculated doses of more than 25%, as shown by the two dose points of 595 cGy and 762 cGy at the edges of the air pocket in Figure 3.25. Root cause (shrink wrap size) was quickly identified from this first clinical measurement, and future NanoFOD fibers were fabricated using shrink wrap of significantly smaller diameter (explained in Section 2.2.5) which were shown to effectively mitigate any air pockets and provided easier identification and localization in the TPS for all subsequent patient measurements.

The second clinical patient measurement was considered as a device failure, since the data tracing did not match the tracings acquired from in phantom measurements. The optical fiber detector was inspected after the treatment and found to be physically broken, indicating that the light propagation during the measurement was compromised and could not be used to calculate the treatment dose. Root cause of the fiber break was not identified, but corrective action was implemented via the
Figure 3.25: Axial CT image of the first patient measurement with the cylinder applicator in place in the vaginal vault. The air pocket created by this over-sized shrink wrap would in theory, allow the tip of the fiber free movement within the range of doses shown. Dose markers, shown here from a screen-shot of Eclipse, characterized the dose gradient across this air pocket to range from about 5.9 to 7.6 Gy, over a distance of just 2.5 mm. Thus, a positioning error of 2.5 mm was shown to lead to a potential dose difference of more than 25% at the possible locations of the NanoFOD phosphor for the first patient.

The creation of a standard operating procedure document (Appendix B). The purpose of this document was to provide guidance on how to conduct a thorough inspection and operational test of all the measurement equipment prior to the patient treatment to prevent additional device failures. In theory, if any fiber was broken prior to being placed in the patient, this new SOP would be able to identify the damage, and allow sufficient time for a different fiber to be used during the procedure. The most important step of this procedure was developed to test fiber integrity; the method used a laser pointer to propagate light from one end of the fiber to the opposite end to verify no gross loss of signal transmission. Since implementing this procedure, all fibers have passed the laser test and no further device failures have been encountered to date. In total, and at the time of this writing, this amounts to more than 55 measurements without an additional device failure.
The dataset acquired using fiber “C11” for a vaginal cylinder applicator treatment is shown in Figure 3.26 with a total of six source dwell positions. For this measurement the source activity was 7.552 Ci, a 590 nm long pass optical filter was used to remove Cerenkov signal, and the fiber was located at 11 cm distance from the base of cylinder and attached directly using Tegaderm.

**Figure 3.26:** (a) Raw data and the corresponding (b) smoothed data from a vaginal applicator NanoFOD patient data measurement. The real time diode voltage was plotted as a function of time, providing knowledge of the scintillator light output throughout the entire brachytherapy procedure. The finite dwells of the source were visible as the discrete steps in the tracing.

After post processing the raw data (Figure 3.26) using the Excel trend line fits to the acrylic fixture calibration data, the NanoFOD measured dose was calculated to be 697.1 cGy (Figure 3.27). In comparison to the TPS value of 670 cGy, this particular treatment represents a 4% difference comparing the NanoFOD to the TPS.

In total, 30 clinical measurements were made for the vaginal cylinder applicator cases, representing the first patient cohort on the clinical trial. The first two patient measurements were not analyzed for dose comparison since the first trial had a large visible air pocket, and the second trial involved the broken fiber, as previously discussed. Additionally, the CBCT scans for fraction 7 were deleted from the
Figure 3.27: Processed clinical vaginal applicator NanoFOD dose measurement using the fixture calibration method combined with the TG-43 dose relationship in water. This figure shows the real time dose rate delivered at any given time from the brachytherapy treatment procedure. The cumulative dose value is shown here as $\int y \, dx = 697.061$ cGy. The red shaded region selects the time interval to compute the cumulative dose, and it could be selectively resized and moved via interactive user input.

Clinical computer system and thus could not be imported into the Eclipse TPS for analysis. Thus, a total of $N=27$ fractions were analyzed comparing the NanoFOD dose to the TPS planned dose. A summary of the clinical trial data is shown in Figure 3.28, with TLDs presented as the gold standard comparison. The average dose ratio comparing to the TPS were 0.98, 1.03, and 1.04 for the NanoFOD, TLD1, and TLD2, respectively. Similarly, the median values were 1.00, 1.01, and 1.02 for the NanoFOD, TLD1, and TLD2, respectively. The quartile 1 and quartile 3 dose values ($Q1/Q3$) for the detectors were 0.935/1.021, 0.993/1.046, and 1.001/1.072 for the NanoFOD, TLD1, and TLD2, respectively.

Thus, only minor variances were found when comparing the NanoFOD system to the TPS planned dose values, and likewise for comparing the TLDs to the TPS dose values. The NanoFOD was found to have a larger inter-quartile range (0.086)
as compared to both TLDs (0.053 and 0.071). A direct comparison of the NanoFOD to the TLD values was not possible, since the TLDs had a larger active volume over which they provided a volumetric average reading in comparison to the NanoFOD.

![Clinical Data (N=27)](image)

**Figure 3.28**: Data from the vaginal cylinder clinical trial showing comparison of the NanoFOD and TLD dosimeters.

A patient by patient data analysis of the NanoFOD is shown in Table 3.5. The best average agreement was 0.0% difference comparing the NanoFOD to the TPS for patient number 9, and the highest variance was -9.2% for patient number 8. Overall, the average measured doses for each individual patient were all under 10% difference compared to the TPS.

The major difficulty encountered with obtaining the TPS dose values for each measurement, was due to the positioning of the dose marker in Eclipse to accurately reflect the location of the NanoFOD phosphor tip. Mammography images were acquired of fibers “C10” and “C11” to provide estimated measurements of the distance of the sensitive scintillation volume relative to the air cavity in the Flexi Needle. These images were used to determine that the sensitive detector volumes of both
fibers were located approximately 2 mm proximal to the end of the hollow-air cavity that was visible in the CBCT HDR planning images due to the Flexi Needle.

The highest variation (NanoFOD vs. TPS) in any single fraction measurement was found to be 19% for fraction number 13. The highest variation for TLDs (vs. TPS) was found to be 18% for fraction number 6, a similar level of variation as the worst case NanoFOD. It has been suggested that a dose threshold discrepancy of >50% should be used for in-vivo detectors when trying to identify treatment errors that may harm the patients, due to the wide variations in reported differences of in-vivo detector dose values in comparison to TPS values (Kertzscher et al., 2014d). The NanoFOD has been shown to perform better than 20% dose accuracy for all measurements tested (N=27), with 50% of the measurements providing dose accuracy within 7% of the TPS. Based on this NanoFOD data, it may be possible to lower the proposed dose threshold error of >50% when using the NanoFOD for brachytherapy.

No clear trend in the NanoFOD dose accuracy as a function of the source activity was observed (Figure 3.29). No clear trend suggests that the SNR was sufficiently maintained across the entire source activity range encountered for clinical
HDR brachytherapy use, and further that the dose calculations were independent of the source activity. Comparing the individual fibers, the average ratio of the NanoFOD C10 vs TPS was 0.94 with an inter quartile range (IQR) of 0.09, and for NanoFOD C11 vs TPS the ratio was 1.01 with an IQR of 0.06. Uncertainty or error in the calibration of NanoFOD C10 may have caused the calculated doses to be systematically lower (6%) than the TPS dose values.

**Figure 3.29:** All individual NanoFOD dose fraction data plotted as a function of the source activity on the day of the measurement. The two clinical NanoFOD fibers used were arbitrarily named “C10” and “C11”.

*Tandem and Ovoid/Ring Applicators*

At the time of this writing all of the raw NanoFOD data has been collected from 30 individual brachytherapy fractions utilizing complex tandem and ovoid/ring applicators. The data reduction and TPS dose values are currently being processed.

3.4 Conclusions

In summary, the experiments carried out here have demonstrated the successful use of the nano-crystalline scintillator based fiber optic detector (NanoFOD) for clinical
measurements in $^{192}$Ir HDR brachytherapy. The device sensitivity was found to be sufficient to achieve accuracy to within 20% of TPS values for all clinical cases, with source strengths ranging from 5-10 Ci. No saturation of the detector signal was achieved, even within 1.5 cm SDD of the clinical source. A working calibration methodology was developed and tested, providing a means of converting the real time voltage to a dose-rate value.

The energy dependence of the yttrium oxide scintillation material was characterized, and methods of mitigation (silver cap) and correction (fixture calibration) were reasonably demonstrated. The Cerenkov signal induced via the “stem effect” was corrected for via the use of an optical band pass filter.

All of these measurements demonstrate that the NanoFOD system offers a unique means of acquiring high resolution dose measurements for HDR gynecologic brachytherapy procedures.
The purpose of this chapter is to highlight the research, development, and characterization of the NanoFOD for its use in small animal dosimetry measurements. A description of the methods and techniques for using this detector to achieve high resolution dose data both in phantom and in mice, will be covered. Experiments were conducted to study the accuracy, energy-dependence, and lifetime effects. Applications of NanoFOD use for in-vivo organ dose measurements, real time small animal image guided radiation therapy, and microbeam radiation therapy were all investigated and the results are reported here.

4.1 Introduction

The two main advantages of the nanocrystalline scintillator based fiber optic detector (NanoFOD) are the (i) real time read out and (ii) small cross sectional size. The optical fiber utilized in the NanoFOD system has a sub-millimeter diameter, making it an ideal candidate for acquiring in-vivo and real-time dose measurements by way of interstitial placement via needles, catheters, and incisions. Further, the yttrium
oxide scintillation material used as the phosphor constitutes a small sensitive volume in comparison to other commercial dosimeters, offering high precision, pin point measurements well suited for the small radiation fields and organ sizes encountered in small animal radiation biology studies.

Commercial alternatives often lack at least one of these two aforementioned criteria: ion chambers are real time but they are too large to be used in-vivo, TLDs are small enough to be placed in-vivo but they require a lengthy and time consuming procedure post-irradiation for signal readout, and MOSFETs are also small enough to be used in-vivo but they do not provide a true “real time” signal. The finite lifetime is the foremost limitation of MOSFETs; MOSFETs can only withstand a total lifetime of about 16,000-20,000 mV (16-20 Gy) (Ehringfeld et al., 2005), after which they should be replaced with new hardware. Radiation aging of MOSFET detectors has been studied by others previously and re-calibration of the detectors is recommended at multiple intervals during use to maintain accuracy (Brady and Kaufman, 2012). Similarly, MOSFETs have demonstrated changes in sensitivity as a function of the radiation source angle, which may exceed > 30% at critical angles (Koivisto et al., 2013; Pomije et al., 2001).

4.1.1 Characterization of NanoFOD for Small Animal Irradiation

To use a radiation detector for dose measurements in small animal x-ray or gamma-ray radiation studies, careful characterization of several important parameters should be performed. These include the (i) depth dose behavior, (ii) dose accuracy in comparison to the gold standard dosimeter, (iii) calibration behavior (i.e. energy dependence, and response linearity vs dose), (iv) angular response characteristics, and (v) lifetime or sensitivity effects that may result from cumulative radiation damage.

Small animal radiation studies at Duke are performed using either orthovoltage x-ray irradiators or isotope based gamma irradiators, such as $^{137}$Cs. For both (i)
x-ray and (ii) gamma type irradiator systems, researchers can deliver a given dose to mice by manually setting the machine exposure time to a specified value. Currently, researchers calculate this exposure time by dividing the total dose that they wish to deliver by a single provided dose rate value. Dose rate values are measured using an ion chamber detector, and are commonly reported for a specific geometry and for a given radiation beam quality. Filters can be selectively used to achieve varying levels of x-ray beam quality on the x-ray type irradiators, providing hardened x-ray spectra. Thus, for dose monitoring and QA for these procedures, knowledge of the NanoFOD device sensitivity and energy response behavior for any given beam was essential.

Recently, more complex small animal radiotherapy techniques have been employed, using small fields and multiple irradiation angles to deliver conformal dose plans to mimic clinical human therapy practices. With increased complexity of treatments, comes increasingly complex quality assurance that physicists should perform to verify accurate dose delivery. For these small animal image guided radiation therapy (SAIGRT) procedures, available commercial radiation detectors often are unable to provide the full range of quality assurance tests, generally requiring multiple detector types to achieve this means.

4.1.2 Microbeam Radiation Therapy

Herein, the development, testing, and use of a novel radiation tool that aimed to provide comparable resolution and accuracy to film along with real-time dosimetry measurements as suited for microbeam and minibeam characterization is described.

Microbeam radiation therapy techniques have been shown to achieve high therapeutic ratios via the use of multiple, parallel, planar x-ray beams with lateral widths of less than 1 mm. Micro-planar x-ray beams are difficult to characterize due to the small lateral beam dimension and the associated steep dose gradient. A tech-
nique is presented that utilized a nano-crystalline scintillator fiber-optic detector (NanoFOD) for real-time measurement of the absolute dose rate and beam profile of a micro-planar x-ray beam generated from a carbon nanotube cathode x-ray irradiator, and the results were compared to Radiochromic film. Due to the real-time readout capabilities, plastic scintillator optical fiber based radiation detectors have been extensively studied for (on-line) radiation measurements for human radiation therapy treatments (Archambault et al., 2007; Beddar et al., 1992b; Beddar, 2006; Moon et al., 2012), but microbeam treatment use of these detectors has not yet been given careful consideration. Applications of optical fiber based detectors studied by others include use for small field radiation measurements, with reports of a 2D scintillator fiber array achieving a 5 mm spatial resolution for field sizes of 1.5x5 cm (Lee et al., 2008). Similarly, a fiber detector constructed from a 5 mm long scintillator has been used to measure radiation fields down to a diameter of 1 cm (Letourneau et al., 1999). These aforementioned optical fiber detectors are too large for microbeam and minibeam RT measurements for measurements of the minibeam widths (0.7 mm) under question.

Translational stages driven by stepper motors have been used to very accurate move silicon strip detectors through radiation fields (Petasecca et al., 2012). Likewise, researchers have used drive screws to translate plastic scintillator based optical fiber detectors through a 10x10 cm electron beam to obtain the 1D lateral dose profile with a resolution of 3.9 mm (Lee et al., 2006a). Adapting this scanning technique demonstrated by others to meet the needs of MRT, required the construction of a scintillation material with substantially reduced dimensions.

To the knowledge of the author, this work demonstrates a first of its kind measurement using an optical fiber based scintillation detector to characterize a minibeam. Further, x-ray dose measurements were achieved using microbeam geometry in a rodentmorphic phantom, to sub-millimeter resolution, and in real time. This study
is entirely made possible by the development and construction of an 11 µm thick, 600 µm diameter nano-crystalline inorganic scintillator based optical fiber (Stanton et al., 2014).

4.2 Methods and Materials

4.2.1 Characterization of NanoFOD for Small Animal Irradiation

The tissue maximum ratio (TMR) (Appendix C.4) response of the NanoFOD was determined by comparison of the raw detector voltage signal relative to the response of both a MOSFET (TN-502RD-H, Best Medical Canada) and an ion chamber (0.18 cm³ RadCal, Monrovia, CA). A series of eight tissue equivalent plastic blocks (CIRS Inc., Norfolk, VA) each of size 150 x 150 x 25 mm were stacked in a column under the x-ray tube of an XRAD-320 small animal x-ray irradiator. In the bottom block, two through holes were drilled to allow for the side-by-side placement of all three detectors (Figure 4.1). The NanoFOD was placed in the smaller hole (3 mm diameter), and the larger hole (14 mm diameter) was used for the ion-chamber and the MOSFET. The central axis of these two holes were located approximately in the center of the block and at the same depth in the material relative to the x-ray tube focal spot. Subsequent measurements were made of the radiation response in all three detectors. After each measurement, one of the blocks was removed from the top of the stack thus leaving the detectors at the same SDD value, but decreasing the thickness of blocks attenuating the primary beam (increasing SSD). This was repeated six times, providing a total of seven measurements all at different tissue attenuation depths. All irradiations were performed using 320 kV tube potential, 2 mm aluminum added filtration, 20x20 cm field size at 50 cm SDD, 10 mA, and 0.2 minute treatment times. The NanoFOD equipment used was the PDF10A femtowatt sensitive diode, and a 600 µm core diameter fiber with 0.22 NA and a 6 mg/7 mm pressed pellet of the nanocrystalline scintillator.
Figure 4.1: Tissue equivalent block phantom geometry enabled increasing quantities of blocks to be stacked above the detector positions, effectively increasing the tissue attenuation depth. The tissue maximum ratio (TMR) measurements were obtained using this setup, since the source detector distance was kept constant for all measurements.

Calibration of the NanoFOD was performed to convert the real time voltage signal of the detector system to a dose-rate value to tissue. For calibration, free-in-air measurements were acquired, using a side-by-side placement of the NanoFOD and a calibrated ion chamber similar to the setup shown in Figure 4.2. The resulting calibration value related voltage to dose rate (cGy/s) at the location of the tip of the fiber where the phosphor was located. The effective point of measurement of the NanoFOD and the ion chamber were located at the same relative distance from the focal spot of the x-ray tube, providing an equivalent radiation environment at the location of each sensitive volume.
Figure 4.2: Effective point of measurement of the NanoFOD was located at the same distance from the x-ray tube as the effective point of measurement of the ion chamber. This calibration was conducted using the XRAD-225Cx with the x-ray tube positioned directly above the table (shooting top down).

The energy dependence of the NanoFOD was determined by acquiring calibrations on the XRAD-320 over a wide range of x-ray tube potentials. The NanoFOD and the ion chamber were located directly on the steel shelf of the irradiator, at an SDD of 50 cm. The x-ray tube potential was then stepped through the range of 40-320 kV in increments of 20 kV, and a simultaneous ion chamber and NanoFOD measurement were made at each kV. The data was then plotted with the y-axis values representing the diode signal per unit dose-rate calibration value (V/cGy/s), with an x-axis value of x-ray tube potential. This experiment was performed using the PDF10A Thorlabs diode and a fiber with three 3 mg/7 mm pressed pellets fixed on the terminus. A 20x20 cm field size was utilized with 2 mm aluminum added filtration. The dose reading for each individual tube potential setting (kV) was calculated based on the specific f-factor value at the average energy of the x-ray beam, as shown in Table 4.1.

For SAIGRT systems, the x-ray tube can rotate 360° around the stage that holds the mouse specimen. When using this geometry, the mouse or the phantom is stationary on the table and so is the radiation detector. Therefore, the use of a radiation detector that exhibits minimal angular dependence is necessary for accurate
Table 4.1: Calculated f-factor values used to convert the ion chamber readings from exposure in air to dose to an ICRU-44 tissue material. The mean energy was estimated using SpekCalc software. For 320 kV, the mean energy was estimated by extrapolating the data points for 300 kV and below.

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<th>Mean E (keV)</th>
<th>f-factor</th>
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dose measurements, with an ideal detector responding in a manner such that only a single calibration value is needed to convert to dose for any arbitrary x-ray tube angle. To characterize angular response of the NanoFOD, two different tests were conducted; one using an acrylic sphere phantom on the XRAD-320 machine at a low energy (120 kV), and a second test using a cylindrical mouse phantom on the XRAD-225Cx at the treatment (225 kV) energy.

The first angular response test of the NanoFOD used an acrylic sphere of 10.16 cm diameter as the phantom in which the NanoFOD was located to simulate a radiation scatter environment. A blind hole drilled in the sphere phantom was utilized to place the tip of the NanoFOD in the exact center. The sphere was positioned on the 50 cm SSD shelf on the XRAD-320, and irradiations were conducted with various rotations of the sphere/NanoFOD phantom. The x-ray was operated at 120 kV,
Figure 4.3: NanoFOD calibration on the XRAD-225Cx was performed free-in-air, alongside a MOSFET and ion chamber detector. (Right) The placement of the NanoFOD and MOSFET were slightly below the effective point of measurement of the ion Chamber (center). Future experiments were performed with the NanoFOD SDD at the same value as the effective point of measurement of the ion Chamber (TG-61 definition of effective point of measurement).

25 mA, 0.3 min exposure time, with a 0.5 mm Cu filter added, and 20x20 cm field size. Measurements were made for two axes of rotation (Figure 4.4): the $\Psi$ axis was tested for a full range of 360° rotation around the axis of the fiber, in increments of 30°, and the $\theta$ axis was tested by rotating the fiber through a range of 180° in increments of 30°.

The second set of angular measurements was performed on the XRAD-225Cx SAIGRT irradiator using a cylindrical mouse phantom (Figure 4.5a) and a 4 x 4 cm square collimator (Figure 4.5b). For comparison, both a NanoFOD and micro-MOSFET detector were located in the hole drilled along the central axis of the cylinder phantom. In-phantom measurements were acquired at tube angles of 0, 90, 180, and 270° for 225 kV with 0.3 mm Cu filtration. Three dose measurements were made at each angle and the absolute doses as computed from applying the correction factors found during calibration were directly compared.

To test the dose accuracy, the NanoFOD and a MOSFET were placed side-by-side in the liver of a sacrificed mouse (Figure 4.6) via a small incision. Prior to these
Figure 4.4: Geometry used for the angular measurements performed in the acrylic phantom.

measurements, calibration was performed using the setup shown in Figure 4.3 and with 5 s of beam exposure time at varying tube current levels of 0, 8, and 13 mA for imaging energy (80 kV with 2 mm Al filtration); and 0, 5 and 8 mA for therapy energy (225 kV with 0.3 mm Cu filtration) as shown in Figure 4.3. Exposure to dose conversion factors were calculated at a mean energy found using SpekCalc software to approximate the x-ray spectrum with the individual filter used. Treatments were delivered to the mouse using a 225 kV (0.3 mm Cu filter) beam with both an open field, and a 4 x 4 cm square collimated field (Figure 4.3), and also at 80 kV (2 mm Al filter) for the open field. The 225 kV treatments delivered approximately 15 cGy, and the 80 kV treatment delivered approximately 8 cGy. It should be noted that the ≈cGy dose level used for these studies was substantially less than the therapy
Figure 4.5: (Left) Planar x-ray image of the NanoFOD and MOSFET placed in the center of a cylindrical mouse phantom (2 cm diameter). (Right) Photograph of the 4x4 cm collimator installed on the x-ray tube of the XRAD-225Cx.

level (Gy) doses typically delivered to mice, but was necessary due to the limitation of the MOSFETs, which burn out with high cumulative doses and require recalibration throughout protracted use.

Additional applications for using the NanoFOD in small animal measurements were investigated. One such study, utilized the NanoFOD as the dosimeter of choice, since other existing dosimeters were too large to provide the needed spatial resolution to meet the goals of the study. Preclinical measurements were performed on the XRAD-225Cx irradiator, in which the biologist wished to partially irradiate orthotopic mammary tumors in mice. The treatment was setup using a square 10 x 10 mm collimator, in which a lead block was positioned in the field to provide a triangular shaped treatment field. 50% of the tumor was located directly in the radiation field, and the other 50% was behind the lead blocked field. The purpose of using the NanoFOD was to achieve high resolution point dose measurements in multiple locations of the tumor, and to study the dose gradients in close proximity.
Figure 4.6: Planar x-ray image on the XRAD-225Cx showing side-by-side placement of the NanoFOD and Micro-MOSFET in the liver of a sacrificed mouse.

to the lead blocked field. To achieve this, a custom tumor phantom was fabricated that mimicked the murine geometry, and allowed placement of the fiber in the tissue equivalent plastic representing the mammary tumors of the mice (Figure 4.7). A tissue equivalent cylinder representing the mouse was also included in the phantom model, to generate realistic scatter as would be encountered during irradiation of the live mice. A 1.1 mm diameter hole was drilled in the mammary tumor phantom to allow placement of the NanoFOD outside the cylinder, but below the plastic tumor structure. The mammary tumors modeled were approximately 1 cm in diameter and could be located at up to 5 mm depth. The target dose to the tumor in the x-ray field was planned to be 15 Gy, and this study sought to confirm this dose prescription
by direct physical measurement.

**Figure 4.7:** (a) X-ray radiograph showing the location of the NanoFOD in the mammary tumor phantom. (b) Photograph of the NanoFOD fiber located in the mammary tumor phantom setup on the treatment stage of the XRAD-225Cx.

Multiple configurations of x-ray field setups (half blocked vs open square 10 x 10 mm collimated x-ray field) were studied, and the geometry for each case is depicted in Figure 4.8. In addition to tumor doses, the NanoFOD was placed in the hole drilled in the central axis of the cylinder to measure doses in the mouse itself. These were used as estimates of the dose to the spine of the mouse. These experiments were carried out over the course of four different days, and a separate NanoFOD calibration was conducted each and every day. The Thorlabs PM100USB/S150C diode setup was used for these measurements.
Figure 4.8: Geometry used for placement of the NanoFOD in various positions of the mammary tumor and the mouse body, with both open field and blocked field setups. Each point dose measured was represented by a letter, “A” through “L” for keeping track of the values.

4.2.2 Microbeam Radiation Therapy

Microbeam Irradiation

The compact microbeam x-ray irradiation system at UNC produced a highly collimated x-ray beam via the use of five linear carbon-nanotube (CNT) cathodes aligned in the length direction. This array of CNT cathodes afforded higher dose rates than could be achieved on a single point cathode design, and fast switching could be achieved by removing the need for thermionic emission. The five cathodes produced field emission of electrons, which were then accelerated via a potential of 160 kV, and were finally focused on a tungsten-rhenium anode target. The resultant x-ray
beam was then collimated using a thickness of 9 mm of tungsten with an aperture of 175 \( \mu m \times 150 \; mm \) (with \( \pm 0.1 \; \mu m \) flatness of the surface) as shown in Figure 4.9. The x-ray beam exited the collimator at 75 mm distance from the focal line array, and the width at the measurement point increased as a function of distance from the focal array.

**Figure 4.9:** Schematic of the scan geometry showing relative orientation of the inorganic scintillation material and the optical fiber detector relative to the x-ray field. Dimensions and geometry of the collimated microbeam are also depicted. Note, diagram not shown to scale.

**NanoFOD Dosimetry and Calibration**

The nanocrystalline scintillator based optical fiber detector (NanoFOD) was fabricated from a 600 \( \mu m \) diameter inner core UV/Vis optical fiber (LEONI Fiber Optics, Inc.) and an inorganic scintillator sensor pellet fabricated from an emissive \([Y_{1.9}O_3;Eu_{0.1},Li_{0.16}]\) nanoscale scintillator composition. One end of the fiber was terminated with the 600 \( \mu m \) diameter, 11 \( \mu m \) thick scintillator sensor pellet (Figure 2.4), while the other end was connected to a PM100USB photo-diode laser power meter and S150C silicon diode (Thorlabs). The diode was connected to a laptop computer.
via USB for real-time data acquisition and display. Using this setup, the detector system was able to record the rate of scintillator light output (in units of watts) due to the incident x-ray radiation field at the location of the scintillator. Sampling rate was set to 20 Hz using the Thorlabs power meter, and the DC level background signal was subtracted from the gross signal level during post-processing of the data. The standard deviation of the acquired raw signal background from the diode and detector system was $6.21 \times 10^{-13}$ W.

Calibration was performed with an open field with the collimator removed from the CNT x-ray system. The purpose of calibration was to convert the collected light emitted via scintillation to a dose to water value. X-ray exposure (R) in air was first measured, and then the necessary f-factor was applied to convert from exposure to dose in water. To calibrate, the NanoFOD was irradiated alongside a NIST-traceable ion chamber (RadCal, Monrovia, CA). The CNT x-ray output was achieved using settings of 160 kV, 8% duty cycle, 30 mA, and 124 mm source to object distance. The effective point of measurements were located at equivalent distances from the x-ray source in accordance with recommendations from AAPM TG-61 (Ma et al., 2001). The cumulative uncertainty from the calibration process was estimated to be 2%; due to the root sum of the square components of 0.46% from the calibration slope value, 0.44% due to the standard deviation observed from repeat measurements, and 1.9% from the University of Wisconsin ADCL calibration of the ion chamber.

The f-factor (Appendix C.4) was calculated according to TG-61 formalism. Calculation of the HVL for the CNT microbeam irradiator was previously described (Beller et al., 2015), yielding a 7.5 mm aluminum HVL and a resulting f-factor value of 0.91 cGy/R (dose to water conversion factor).
Experimental Measurement Geometry

For the dosimetry measurements the collimation was reinstalled on the CNT x-ray system, and the NanoFOD was placed in the center along a hole drilled in the axis of a cylindrical mouse phantom (CIRS Inc., Norfolk, VA) made of tissue equivalent plastic. A clamp was used to attach the entire phantom/fiber assembly to a translation stage (Newport Corporation) capable of 0.1 µm minimum incremental motion (Figure 4.10). The angle of the collimated microbeam was 8° off perpendicular. The orientation of the scintillation material was setup in a similar manner to the “edge-on” MOSFET technique (Kaplan et al., 2000), in which the smallest dimension of the material was oriented parallel to the beam (Figure 4.9) to provide the highest resolution measurement.

The stepper motor was controlled via software to translate at a constant rate of 3.136 µm/s, in effect sweeping the phantom and fiber assembly from right-to-left through the plane of the microbeam in a direction oriented along the axis of the fiber. Similar to calibration, the x-ray was operated at 8% duty cycle, 30 mA, and 160 kV.

Experimental film measurements were made as the gold-standard measurement, by which all NanoFOD measurements were compared to. The film calibration and irradiations were all carried out by the UNC research team, and for a full description of the methods and materials the reader is referred to (Hadsell Jr, 2013; Belley et al., 2015). The beam full width half maximum and the peak dose rate were characterized using the radiochromic film. It should be noted that the source-detector-distances were slightly different for the film measurements as compared to the NanoFOD measurements, but the difference was accounted for as explained in the results and discussion section.
Figure 4.10: The optical fiber (NanoFOD) detector was placed along the Z-axis of the cylindrical mouse phantom. The mouse phantom was then clamped (green hardware) to a translational stage, to enable motion in a direction perpendicular to the long axis of the microbeam. The stage moved from right-to-left, enabling the smallest dimension of the scintillator pellet to be used to measure the microbeam width.

4.2.3 $^{137}$Cs Lifetime Test

The NanoFOD was placed at carousel position #1 on the Mark I-68A $^{137}$Cs irradiator (JL Shepherd and Associates, San Fernando, CA) alongside an ion chamber and exposed to in excess of 1.6 kGy dose at approximately 15.2 Gy/min dose rate. The raw signal readout from the NanoFOD coupled to the Thorlabs PM100USB/S150C diode was recorded for the entirety of the irradiation, and the slope value of the data
was measured to look for changes in light output as a function of the cumulative dose.

4.3 Results and Discussion

4.3.1 Characterization of NanoFOD for Small Animal Irradiation

The TMR data (Figure 4.11) results found the NanoFOD percent difference as compared to the MOSFET reached a maximum of 4.4% at 22.9 cm TMR depth, and a maximum difference of 7.4% as compared to the ion chamber at a TMR depth of 17.8 cm. The average percent difference in TMR values was 4.2% comparing the NanoFOD to the ion chamber, and was 0.9% comparing the NanoFOD to the MOSFET for the 7 depths tested. The NanoFOD agreed with the MOSFET value to within 5% for all depths, suggesting the depth dose response of the NanoFOD was similar to the MOSFET. At the largest depth of 33 cm, the NanoFOD vs. MOSFET difference was -2.1% and the NanoFOD vs. ion chamber difference was 0.1%. Differences in relative detector responses as a function of depth did not show any major systematic differences, as the agreement at the deepest TMR value was found to be within 2% for all detectors.

The calibration values as a function of the x-ray tube potential (kV) are shown in Figure 4.12. At 40 kV the SNR was 8.2 at a dose rate of 2.63 cGy/min, and at 320 kV the SNR was 302.0 at a dose rate of 219.13 cGy/min. Highest sensitivity of the NanoFOD system was achieved at 100 kV corresponding to an average photon energy of just under 50 keV. The theoretical maximum (saturation of diode) detectable dose rate would be achieved at 4 Gy/min dose rate with a 100 kV configuration, however lower sensitivity diodes and less scintillator material in the fiber construction would allow for creation of a system with a higher limit of dose rate.

The calibration data for a 120 kV and a 320 kV beam are shown in Figure 4.13. Higher light output per unit dose was seen for the lower energy beam, most likely
Figure 4.11: TMR data for three different detectors in a tissue equivalent block phantom, under 320 kV x-ray irradiation.

Figure 4.12: NanoFOD sensitivity characterized over a range of x-ray tube potentials. Maximum light output per unit dose was achieved just below an average x-ray energy of 50 keV, at an x-ray tube potential of 100 kVp.
due to increased photoelectric events in the high-Z phosphor. Both linear fits had R² values greater than 0.99.

![Figure 4.13: Linear calibrations of the NanoFOD system with the PDF10A diode achieved by varying the tube current at two x-ray energies on the XRAD-320, using 2 mm aluminum added filtration. No saturation of detector signal or loss of linearity was observed even for dose rates in excess of 2 Gy/min. 2 Gy/min likely represents the upper limit of dose rates used for small animal studies on these irradiators.](image)

The spherical phantom angular response measurements at 120 kV are shown in Figure 4.14. The Ψ = 0° and Ψ = 360° points represent one full rotation, and the measurements agreed within 2.2%. This 2.2% value may indicate the amount of random error in the measurement possibly due to (i) the inability to exactly replicate the geometry after the repositioning of the sphere phantom after rotating it the full 360 degrees, or (ii) due to the repeatability of the measurement inherent to the NanoFOD system. Treating all measurements as independent, the average integrated diode signal was 4.12 V-s, and the coefficient of variation was 3.6% across all 20 measurements. The maximum deviation (11%) from the mean value was found to occur at Ψ = 90°. Averaging three gross signal levels for the same rotation angle to test NanoFOD repeatability yielded an average net signal level of 0.2687 V and had a
COV of 0.08%, indicating high repeatability and stable background signal level across the three repeated irradiations. Looking at the average gross signal level of 0.2687 V, the background noise standard deviation was 0.0094 V, yielding a calculated SNR of 28.5. High sampling rate allowed for the averaging of N=400 data points to estimate the mean signal level of the steady state signal during each irradiation, leading to a standard error of the mean signal level for a 0.3 min irradiation of just 0.18%.

**Figure 4.14:** Data for the angular response of the NanoFOD system about two different axes at 120 kV.

For the second angular test the NanoFOD calibration was shown to be linear for both 80 kV and 225 kV on the XRAD-225Cx (Figure 4.15). Results in the mouse phantom showed a variance of 1% across 0, 180, 270, and 360° x-ray tube positions calculated as half the difference of the min and max values divided by the mean. This measurement was repeated at the imaging energy (80 kV with 2 mm Al filter), and the calculated value was 9%. According to this data, the NanoFOD exhibited superior angular performance at higher x-ray energy.

The MOSFET and NanoFOD dose values were consistently within 3% of each other for the range of angles tested at 225 kV when located in the cylinder mouse.
Figure 4.15: Calibration data for the NanoFOD use on the XRAD-225Cx at two energies, using the Thorlabs PM100USB/S150C diode (y-axis units are calibrated to energy from the manufacturer). The $R^2$ value was >0.9999 for both cases, after fixing the y-intercept to 0.

phantom (Table 4.2). The XRAD-225Cx machine appeared to have increased output for the 180° beam angle, a finding that also appeared in data acquired in later studies.

Table 4.2: Data comparison of the NanoFOD and micro-MOSFET at 225 kV in the cylindrical mouse phantom. The uncertainty is given as the standard deviation ($\sigma$) value of three repeat measurements. The difference column reports the percent difference of the NanoFOD and the MOSFET detectors.

<table>
<thead>
<tr>
<th>Angle (deg)</th>
<th>MOSFET (cGy)</th>
<th>MOSFET ($\sigma$ cGy)</th>
<th>NanoFOD (cGy)</th>
<th>NanoFOD ($\sigma$ cGy)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.56</td>
<td>0.27</td>
<td>7.59</td>
<td>0.45</td>
<td>-0.4%</td>
</tr>
<tr>
<td>90</td>
<td>7.70</td>
<td>0.25</td>
<td>7.69</td>
<td>0.61</td>
<td>0.0%</td>
</tr>
<tr>
<td>180</td>
<td>7.85</td>
<td>0.21</td>
<td>7.75</td>
<td>0.57</td>
<td>1.3%</td>
</tr>
<tr>
<td>270</td>
<td>7.66</td>
<td>0.19</td>
<td>7.63</td>
<td>0.10</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

At 225 kV in the liver of the mouse, the dose agreement between the NanoFOD and the MOSFET was within $\approx 1\%$ for both the collimated and the open field x-ray (Table 4.3). At 80 kV a 14% disagreement between these two detectors was observed, however the absolute difference in this value was only on the order of 1 cGy. This
80 kV case should be tested in the future to higher absolute doses and with an independent calibration to see if better agreement is reached.

Table 4.3: Data comparison of the NanoFOD (labeled “Nano”) and micro-MOSFET at 225 kV and 80 kV in the liver of a sacrificed mouse. The uncertainty (σ) is given as the standard deviation value of three repeat measurements. The difference column reports the percent difference of the NanoFOD and the MOSFET detectors.

<table>
<thead>
<tr>
<th>Collimator</th>
<th>kV</th>
<th>MOSFET (cGy)</th>
<th>MOSFET (σ cGy)</th>
<th>Nano (cGy)</th>
<th>Nano (σ cGy)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4x4cm</td>
<td>225</td>
<td>15.44</td>
<td>0.47</td>
<td>15.27</td>
<td>0.47</td>
<td>1.09%</td>
</tr>
<tr>
<td>Open</td>
<td>225</td>
<td>16.44</td>
<td>0.35</td>
<td>16.45</td>
<td>0.62</td>
<td>-0.03%</td>
</tr>
<tr>
<td>Open</td>
<td>80</td>
<td>7.66</td>
<td>0.10</td>
<td>8.75</td>
<td>0.24</td>
<td>-14.21%</td>
</tr>
</tbody>
</table>

For the experiments conducted over the course of four days on the XRAD-225Cx with the mammary tumor phantom, findings indicated that despite using the identical hardware for each of the experiments, that the light output per unit dose calibration factor (Figure 4.16) was changing considerably (19%) between repeat experiments. Through a series of extensive trial and error, root cause was determined to be bending of the optical fiber causing differences in signal loss of the primary scintillation signal. This process of optical power loss differs from that of frustrated total internal reflection (FTIR), where FTIR is caused by the addition of a third medium with higher refractive index than the fiber cladding, causing the evanescent wave to transmit power into the third medium. Instead, when the fiber was routed into the irradiator housing via the side access port, any considerably small bends (radius <5 cm) were causing optical power loss. Due to differences in the day to day setups, the fiber bending (and thus the loss) was different each time the NanoFOD fiber was routed into the irradiator housing. However, by calibrating the detector system on each experiment day, the fiber losses were taken into account in the calibration files. Therefore, as long as the optical fiber was not repositioned in the irradiator access port, the calibration was valid for the successive irradiations performed on that same day.
The dose point measurements for all of the mammary tumor treatment geometries are displayed in Table 4.4. The point dose values across all four days of experiments were found to agree to within ±6% as long as the calibration was applied from the same day of the experiment. Measurements were found to have coefficient of variation (COV) of 3.2% and 4.1% comparing the results from experiment one to three, and one to four respectively. Considering uncertainty on the calibration slope values of ≈2%, and any additional uncertainties that may have manifested due to geometrical setups, repeatable and accurate NanoFOD dose measurements were indicated by the 6% agreement value. For the planned target dose of 15 Gy in the radiation field, these QA measurements reported physical confirmation via the measurement of 14.28 and 15.37 Gy, indicating accurate dose was prescribed and delivered to these tumor sites in the mice. The SNR value when the NanoFOD was in the radiation field
was greater than 75, and was less than 1 when the NanoFOD was behind the lead
blocked field.

Table 4.4: NanoFOD measured point dose values in a mammary tumor phantom for
all setups shown in Figure 4.8. The † symbol indicates that the dose rate was below
the typically quoted minimum detectable dose rate of the NanoFOD (0.05 cGy/s).
The * symbol indicates that this point was not physically measured, but it can
estimated that this dose would be between the dose of point ‘A’ and point ‘L’ (14.72
and 15.37 Gy). Data collected on the second day of experiments (Exp 2) was omitted
from analysis because it showed substantial asymmetries in the irradiation and larger
uncertainty in the calibration slope value, which were theorized to have occurred due
to poor setup geometry of the mouse phantom relative to the irradiator isocenter.

<table>
<thead>
<tr>
<th>Point</th>
<th>In x-ray Field (Yes/No)</th>
<th>Block (Yes/No)</th>
<th>Dose Exp 1 (Gy)</th>
<th>Dose Exp 3 (Gy)</th>
<th>Dose Exp 4 (Gy)</th>
<th>% Diff</th>
<th>Standard Deviation (Gy)</th>
<th>COV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Y</td>
<td>Y</td>
<td>14.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Y</td>
<td>N</td>
<td>13.39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>N</td>
<td>N</td>
<td>0.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>N</td>
<td>Y</td>
<td>0.07†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Y</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Y</td>
<td>N</td>
<td>14.91</td>
<td>14.28</td>
<td>-4.2%</td>
<td>0.45</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Y</td>
<td>Y</td>
<td>14.58</td>
<td>15.48</td>
<td>6.2%</td>
<td>0.64</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Y</td>
<td>Y</td>
<td>11.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>N</td>
<td>Y</td>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>N</td>
<td>Y</td>
<td>0.48</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Y</td>
<td>N</td>
<td>15.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.2 Microbeam Radiation Therapy

Calibration

For the CNT microbeam irradiator the linear slope of the NanoFOD light-output
to exposure (in air) conversion value was calculated as $2.054 \times 10^{-12}$ J/R, with
$R^2=0.9997$ (Figure 4.17). After dividing the calibration slope by the f-factor found
using TG-61, the final light-output to absorbed dose to water conversion factor was
calculated to be $2.257 \times 10^{-12}$ J/cGy.

126
Figure 4.17: NanoFOD integrated optical power response characterized over a range of cumulative 160 kV x-ray exposures on the UNC CNT microbeam system. The collimation was removed during calibration to enable side-by-side irradiation of the NanoFOD and ion chamber.

**Peak Dose Rate and Beam Profile**

Due to the nature of the linear light output with increasing dose rate, the real time diode data was converted from net power (J/s) to net dose rate (cGy/s) by dividing the data by the conversion factor of $2.257 \times 10^{-12}$ J/cGy. The time-stamped data acquired and stored during the scanning of the x-ray beam was later analyzed and appropriately displayed with the dose-rate encountered by the optical fiber detector. Further, this raw data that was collected in real-time was multiplied by the translation speed of the stage to provide spatial information about the location of the tip of the optical fiber during the scan of the beam profile, as shown in Figure 4.18. Due to the inherent noise in the data, a rectangular filter with width 0.55 s (11 data points) was convolved with the raw data to provide a smoothed beam profile.

Analysis of the calibrated data allowed for direct calculation of both the peak dose
Figure 4.18: Raw (black) and smoothed diode data (red) resulting from the scanning of the x-ray microbeam with the NanoFOD system. Axes shown in blue represent calculated values, after applying calibration for dose rate (right axis) and the translation stage movement speed to find the position (top axis). Time 0 s indicated the right edge of the x-ray beam, and time 300 s represented the left edge.

rate (1.91 ± 0.06 cGy/s) and the beam FWHM (420 µm) as displayed in Figure 4.19.

Comparison to Gold Standard - Radiochromic Film

The film measured the peak dose rate to be 1.16 Gy/min at a source to object distance of 124 mm and due to the attenuation of 1.1 mm of acrylic. To account for the attenuation profile of the the mouse phantom and the NanoFOD source to object distance of 117 mm, TMR corrections were applied to the film data to provide equivalence for comparison to the NanoFOD geometry. The resulting film dose rate was adjusted by a combined factor of −3.9% from findings of TMR table comparisons (TMR=0.974 for 1.1 mm acrylic, TMR=0.853 for 10 mm mouse radius) and the falloff of a line source with increasing distance from the anode as previously measured by experiment (factor of 1.1 needed for correction).

A comparison of the gold standard (radiochromic film) to the NanoFOD system is summarized in Table 4.5. The NanoFOD measured dose rate was approximately
2.7% higher than that measured by film. The magnitude of this difference was within the experimental uncertainties of the NanoFOD (2%) and on par with the uncertainty of radiochromic film as reported by others (Bräuer-Krisch et al., 2009). Thus, the data collected here supports the use of the NanoFOD for the accurate measurement of the peak dose rate in MRT for x-ray beams with comparable FWHM and geometry as the CNT x-ray system.

Table 4.5: Comparison of the radiochromic film measured values and NanoFOD values for the characterization of the CNT MRT x-ray irradiator system. Note, film dose rates were adjusted by -3.9% to account for differences in setup and geometry between conditions of film and NanoFOD irradiations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radiochromic Film</th>
<th>NanoFOD</th>
<th>Percent Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Dose Rate (cGy/s)</td>
<td>1.86 ± 0.15</td>
<td>1.91 ± 0.06</td>
<td>2.7%</td>
</tr>
<tr>
<td>FWHM (µm)</td>
<td>320</td>
<td>420</td>
<td>31%</td>
</tr>
</tbody>
</table>

Concerning the FWHM value as measured by the NanoFOD (420 µm) in comparison to film (320 µm), a difference of approximately 31% was observed. Considering the differences of film (2D detector, no scanning of the beam) in contrast to the

Figure 4.19: Characterized lateral beam profile of the x-ray microbeam from the UNC CNT MRT system. Data displayed here was smoothed using a rectangular filter with width of 0.55 s.
NanoFOD (3D detector, scanning of the beam) the modest disagreement observed did not come as a surprise. Additionally, volumetric effects of the 11 µm width of the scintillator volume combined with the 8° x-ray beam angle with respect to vertical were theorized to induce “blurring”, manifested as the measured difference of 100 µm in the reported FWHM of the beam profile. Thus, as depicted in Figure 4.20, the NanoFOD did not provide a true “point-dose” measurement of the microbeam for each instantaneous point in time during which data was sampled.

In theory, one could remove the effect of the volumetric blurring induced by the scintillator volume. However, simple de-convolution with the point-spread-function (PSF) of the detector is a difficult task, since the system was not necessarily linear shift invariant (LSI) and the PSF of the detector is not known. The reason the system may not be LSI may be attributed to the expected changes in geometry that are dependent on the translational position of the scintillator relative to the x-ray beam, and the potential resulting differences in light collection via the aperture of the optical fiber (Figure 4.20). Spatial changes in sensitivity and light collection via the optical fiber were not accounted for during calibration, as calibration irradiated the entire scintillator volume.

Additionally, the modest difference in measured FWHM for the NanoFOD and film may be explained due to differences in the material properties of these two detector mediums. X-rays at an energy equal to the mean beam energy (60 keV) after undergoing a 90° Compton scatter event in the tissue material would have an energy of 53.7 keV and a calculated mean free path (MFP) that was 87 times shorter in the yttrium oxide scintillator as compared to the near tissue-equivalent film material (Arjomandy et al., 2010). In tissue the MFP (4.6 cm) at this energy was much larger than the overall beam dimension, indicating that the majority of scattered photons deposited dose at large distances away from the primary beam. However, in the scintillator material of the NanoFOD, the MFP (0.05 cm) was similar in size to
Figure 4.20: Depiction of the volumetric effects of partial irradiation of the scintillation volume and geometry dependent effects due to the angle of the microbeam. Spatial changes in sensitivity and light collection via the optical fiber were not accounted for during calibration, as calibration was provided by irradiation of the entire scintillator volume.

the beam dimension, suggesting that a large fraction of scattered x-ray energy was measured in the penumbra region of the primary radiation beam. The NanoFOD measurement therefore may have measured increased dose in the penumbra, which may have led to the difference in measured FWHM compared to film.

Conceivably, the measurement technique demonstrated here on a single microbeam could be scaled to apply to a planar microbeam array, in which multiple x-ray beams are utilized to simultaneously cover a larger treatment area. Further work is needed to demonstrate the utility of the NanoFOD for PVDR measurements in these multi-beam geometries, since the valley dose rate was not characterized in this study.

4.3.3 $^{137}$Cs Lifetime Test

The lifetime test results (Figure 4.21) showed no change in the measured photo-diode signal for the duration of the 1600 Gy dose. One limitations of this study was that there may have been a small component of Cerenkov radiation generated in the fiber itself. In the future, this experiment should be repeated using the PDF10A diode
with the optical band pass filter to remove any Cerenkov signal.

![Cs-137LifetimeTest:1.6kGyTotalDose](image)

**Figure 4.21:** Data from the $^{137}$Cs lifetime test, conducted by delivering protracted radiation exposure to the NanoFOD alongside an ion chamber. Cumulative dose delivered was in excess of 1600 Gy.

### 4.4 Conclusions

This work presents a novel detector device, opening up new possibilities for in-vivo dose measurements and real time measurements for small animal, microbeam, and minibeam radiation devices. The NanoFOD exhibited linearity over a broad range of dose rates, real time capabilities, dose accuracy, limited angular dependence at treatment energies, and resistance to radiation damage. The potential use of the NanoFOD system for small animal x-ray irradiation provides advancements by significantly reducing the amount of time necessary for characterization of the dose properties of small x-ray field sizes, in comparison to detectors such as film and TLDs.
When it comes to accuracy, Monte Carlo particle transport simulation is considered the gold standard for high resolution dosimetry, especially for situations where physical detectors can not be reliably used (Hissoiny et al., 2011; Bakhtiari et al., 2010; Apipunyasopon et al., 2013; Morales et al., 2014; Semenenko and Stewart, 2004). This chapter is devoted to Monte Carlo analysis of organ doses in mice for whole body x-ray irradiation. Clinical treatment planning for human radiation therapy, establishes the target dose as well as the dose distribution to a specific location. However, this has generally not been implemented in small animal research. A new dose prescription method is proposed here for small animal radiation studies, and compared to the conventional approach of assigning a single dose value for irradiation of the entire mouse. The goal was to study a more comprehensive approach of characterizing individual organ doses to minimize the resulting error and uncertainty.

5.1 Introduction

Medical research relies heavily on preclinical small animal experiments to test safety and efficacy of drugs and medical devices, prior to use in humans (Augustine et al.,
Murine models are a popular choice for studying radiation countermeasures and radiation therapy treatment techniques since these models provide a cost effective way for researchers to work with large clonogenic sample sizes. To achieve consistent results in small animal radiation therapy studies, great emphasis is given to minimizing the uncertainty in the calculated radiation dose, as this is one of the parameters of a radiation biology study that can be carefully monitored and controlled (Williams et al., 2010).

Dose response curves seek to determine the magnitude of an effect as a function of the absorbed dose. These curves are often used to estimate risk thresholds or functional endpoints in a target organ location. Oftentimes, small changes in the absorbed dose lead to large changes in the incidence rate of an effect. For these cases, the importance of accurate dosimetry to the target location can not be overstated. Current methods of dosimetry generally make the false assumption that biological irradiators will deliver a uniform and homogeneous dose profile throughout the entire mouse. This false assumption drives the need for the development of new dose prescription techniques that provide accurate dose to a target organ location when irradiating small animals.

The focus of this study was on orthovoltage x-ray irradiators for whole body, mouse irradiation. Whole body irradiation is commonly used for experiments that require a large number of irradiations due its speed and simplicity. This is in contrast to studies that use Small Animal Image Guided Radiation Therapy (SAIGRT) machines, which limits the number of animals that can be used in a study due to the time intensive process of the setup and treatment of each individual mouse specimen in the study.

Further, x-ray irradiators were an appropriate choice of irradiator type for this study due to increasing popularity. Recent attention given to national security has made the use of isotope type irradiators (\(^{137}\)Cs and \(^{60}\)Co) more costly and cumber-
some to maintain and operate due to the perceived threat of terrorist actions (Borchardt, 2008). The radiation type and energy of orthovoltage x-rays (polychromatic, $<$320 kV energy range) as compared to gamma rays from isotope decay (monoenergetic, $>$600 keV energy range) lead to differences in dose distribution, dose rate, and overall operation methods of these two types of irradiators. Moreover, x-ray irradiators have various parameters that can be changed such as kV, filtration, mA, and field size – leading to many possible configurations that may affect dosimetry such as the x-ray beam quality and dose rate. Considering the increased complexity for x-ray type irradiators, understanding of the dosimetry and proper operation is necessary to deliver an accurate and appropriate dose.

While others have studied dose distributions in mice for both (i) low kV polychromatic spectra (120 and 225 kV) and for (ii) low and high energy monoenergetic photons up to 1250 keV, realistic whole body mouse simulations have not performed at 320 kV tube potential (Chow et al., 2010; Wong et al., 2008; Bazalova et al., 2009; Chow and Leung, 2007; Chow, 2012). In this study the accuracy of the conventional dose prescription method was evaluated, which delivers the prescription dose to a mouse using a single dose rate measurement to calculate the irradiation time given by:

$$ t = \frac{D_T}{D_M} $$

Where $t$ is the calculated irradiation time, $D_T$ is the target dose that is prescribed, and $D_M$ is the measured dose rate. For a target dose of $D_T = 4$ Gy and with a measured dose rate of $D_M = 1$ Gy/min, the user would be advised to irradiate mice for a total of 4 min.

Monte Carlo will be used along with the MOBY mouse phantom (Figure 5.1) (Segars et al., 2004) to calculate organ doses and to quantify the dosimetry error that can arise due to neglecting to calculate organ specific doses when irradiating mice on
the XRAD-320 (Precision X-ray, North Branford, CT) small animal irradiator. The results presented here are not intended to be used as a dose lookup table, since actual dose values will vary depending on the individual experimental setup and geometry.

Figure 5.1: MOBY mouse phantom renderings. 3 cross-plane views and 3D rendering created from the x-ray CT attenuation data provided as output from the MOBY software.

5.2 Methods and Materials

The Geant4 Application for Tomographic Emission (GATE) toolkit was used to perform the dosimetry. GATE is a toolkit for the high energy physics particle transport code Geant4 (Ivanchenko et al., 2003), allowing easy setup of medical physics dosimetry simulations (Jan et al., 2011; Buvat and Lazaro, 2006; Strul et al., 2003; Jan et al., 2004). GATE has been validated for low energy photon dosimetry simulations, and has been commonly used for nuclear medicine studies of positron emission tomography and single photon emission computed tomography (Taschereau et al., 2006; Thiam et al., 2008; Flux et al., 2006). Additionally, GATE has been used for dosimetry studies in mice for 80 kV imaging procedures (Taschereau et al., 2006). In this study, GATE v6.2 was used with the physics settings shown in Table 5.1.
To obtain high resolution dose results, default physics parameters were modified to allow for lower energy secondary particle production. Examples of these changes were setting the electron cut value to 0.01 mm from the default of 1 mm. In muscle tissue this 0.01 mm electron cut corresponded to the energy production threshold of 15 keV, below which, no secondary particles were generated or tracked. Since the phantom utilized sub-millimeter voxel sizes, these modified electron cut values increased accuracy of the dose deposition while simultaneously providing a reasonably fast computation time. The Livermore physics models were chosen since they were validated in the energy range of 250 eV to 100 GeV, as opposed to the default Standard Model physics processes, validated for 1 keV to 100 TeV.

Table 5.1: Physics settings used in the Monte Carlo dosimetry simulations performed in GATE.

<table>
<thead>
<tr>
<th>Process</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photoelectric</td>
<td>Livermore</td>
</tr>
<tr>
<td>Electron ionization</td>
<td>Standard</td>
</tr>
<tr>
<td>Bremsstrahlung</td>
<td>Standard</td>
</tr>
<tr>
<td>Compton scatter</td>
<td>Livermore</td>
</tr>
<tr>
<td>Rayleigh scatter</td>
<td>Livermore</td>
</tr>
<tr>
<td>e- e+ Multiple scatter</td>
<td>Urban93</td>
</tr>
</tbody>
</table>

The small animal irradiator that was modeled in all of the Monte Carlo simulations was the XRAD-320, an orthovoltage x-ray irradiator cabinet capable of producing a 320 kV beam at 10 mA tube current. Different filters were available from the manufacturer to allow the user to generate x-ray spectra with different beam qualities achieved by beam hardening (Table 5.2). Most commonly, filter B (2 mm Al) and C (0.1 mm Cu + 2.5 mm Al) are used at Duke to obtain an x-ray beam that has a moderate amount of beam hardening, ensuring an increased average energy compared to the unfiltered beam. Simultaneously, these filter choices allow for a moderately high dose rate, allowing for shorter irradiation times compared to filter D (0.8 mm Sn + 0.25 mm Cu + 1.5 mm Al). The x-ray field size was 20 x
20 cm² at a source-to-shelf distance of 50 cm. The original equipment manufacturer (OEM) shelf was 3 mm stainless steel, used to hold samples during irradiation.

Table 5.2: Manufacturer provided filters, available for the XRAD-320 machine.

<table>
<thead>
<tr>
<th>Filter Name</th>
<th>Filtration Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.65 mm Al</td>
</tr>
<tr>
<td>B</td>
<td>2 mm Al</td>
</tr>
<tr>
<td>C</td>
<td>0.1 mm Cu + 2.5 mm Al</td>
</tr>
<tr>
<td>D</td>
<td>0.8 mm Sn + 0.25 mm Cu + 1.5 mm Al</td>
</tr>
</tbody>
</table>

Monte Carlo transport codes require geometry and material definitions of the sample that is irradiated. For this purpose, the MOBY mathematical mouse phantom was used as the whole body input, extensively used by others in GATE simulations (Taschereau and Chatziioannou, 2008; Lee et al., 2013; Silva, 2010). Similarly, voxelized phantom models have been commonly used for Monte Carlo dosimetry studies, such as for calculating organ dose conversion values (S-factors) in mice for studying radionuclides (Stabin et al., 2006; Bitar et al., 2007; Larsson et al., 2007). Mouse sizes of 33 g (MOBY default), 23 g, and 12 g were studied by scaling the voxel sizes of the phantom, resulting in isotropic cubic voxels (256x256x800) of length 0.145 mm, 0.1036 mm, and 0.1286 mm, respectively.

Two output files were used from the MOBY phantom (Figure 5.2): (a) a photon attenuation dataset used for the spatial map of the atomic composition and density of materials, and (b) an output file (radioactive nuclide source activity) manually set to provide integer value outputs corresponding to known individual organs. These unique integer values allowed for binary-mask segmentation and tallying of the dose in all organs within the MOBY phantom.

Geant4 v.9.4p02 was used to simulate the x-ray tube output from the XRAD-320 machine. According to manufacturer provided specifications, the x-ray tube was modeled and the photon energy and fluence rate of the bremsstrahlung radiation was measured after bombarding the tungsten anode target with 320 keV monoenergetic
The MOBY phantom was used to define the (a) material definitions for dosimetry derived from photon attenuation data, (b) anatomical definitions of organs derived from the source activity output, and (c) corresponding organ masks such as the lung mask.

Electrons. The emitted bremsstrahlung photons were scored by a detector at 50 cm SSD, and binned by energy. The results from placing materials representative of three filters (A, B, and C) between the anode and the sensitive detector are shown in Table 5.2.

For the Gate dosimetry simulations, dosimetry actors were utilized to score the dose in voxels (dosels) with the same resolution and position as the input phantom anatomy. The MOBY binary mask data (Figure 5.2C) for each organ was matched to the corresponding dose output, and the organ doses were computed throughout the MOBY phantom. Careful consideration was given to calculating the dose to the red bone marrow, in accordance with the homogeneous bone marrow approximation (HBA). The HBA uses the dose delivered to a homogeneous mixture of skeletal tissue.
as an estimate of the dose to the marrow (Lee et al., 2006b). Additional simulations were later performed using higher resolution images of the trabecular bone structure to improve on the accuracy of dose estimation in the bone marrow compartment, and are discussed in Chapter 6.

X-ray spectra output from the Geant4 simulations of the XRAD-320 were used as the source input definition for the Gate dosimetry studies on the MOBY mouse. In this manner, the energy and relative emission frequency of the polychromatic x-ray spectra were accurately accounted for in the dose simulations. $4 \times 10^9$ source particles were simulated, requiring about 35 CPU-days of simulation time on an Intel i7-3820 CPU (9 days in total due to parallelization to the quad core architecture).

In the simulation geometry a single MOBY mouse phantom was centered at 50 cm distance from the focal spot of the x-ray tube, representative of the XRAD-320 geometry. The mouse was positioned prone so that the x-ray beam entered on the dorsal side. No machine shielding was included in the simulations. GATE simulations were also performed to study the effect of the backscatter generated by the 3 mm steel shelf, placed on the ventral side of the phantom. The organ dose results reported here did not incorporate the 3 mm steel shelf in the simulation, as the 3 mm steel shelf was found to produce negligible changes in calculated relative organ dose values.

The beam qualities found by Geant4 Monte Carlo simulation were validated with physical measurements on the XRAD-320 machine. Half Value Layer (HVL) values were found using Monte Carlo by systematically increasing thickness of copper material between the simulated anode and a sensitive detector that recorded dose to water. Similarly, the physical experiment utilized copper filters placed under the x-ray tube, and physical ion chamber measurements were made to find the thickness of filters needed to attenuate the air kerma rate to a resulting rate that was half the initial value. The ion chamber (RadCal, Monriva, CA) was 6 cm$^3$ volume and was
placed free-in-air at 50 cm SDD for the HVL measurements. Due to the similarity between filters A and B, only filters B and C were considered for the HVL study.

For the measurements to determine the effect of the 3 mm stainless steel shelf on backscatter, two sets of physical ion chamber measurements were performed; one when a 0.18 cm³ ion chamber (RadCal) was placed directly on the steel shelf, and one performed at the same height with the chamber placed on Styrofoam (free-in-air geometry). In addition, a Monte Carlo study was performed to measure the dose deposition in a 1 x 1 x 1 cm³ volume of water placed on a simulated 3 mm steel shelf, and then again free-in-air.

5.3 Results

The x-ray spectra obtained from the Geant4 simulations of the various filter types are shown in Figure 5.3 and compared to the “open” (no filter) case. Average energy values of the spectra were found to be 71, 81, 85, and 94 keV for the open, A, B, and C filtered beams, respectively.

The experimental beam attenuation measurements used to find the HVL of the 320 kV beams are displayed in Figure 5.4. The HVL values given in units of mm copper were found to be 1.04, 1.06, and 1.43 mm for the filters A, B, and C, respectively. The Monte Carlo studies found that 1 mm copper added to the beam produced using filter A and B attenuated the beam to a dose ratio of 0.453 ± 0.001, and the addition of 1.4 mm Cu added to the beam produced using filter C attenuated the beam to a dose ratio of 0.477 ± 0.003.

Monte Carlo results showed an increase in the absolute dose values in the MOBY phantom due to the inclusion of the 3 mm stainless steel shelf in the simulation, but after normalization, the effect of backscatter was found to not lead to any substantial differences in the calculated relative organ dose values. The increase in absolute dose was found to be 1.8% averaged over all the organs for filter B [minimum organ
Figure 5.3: Relative energy spectra, showing relative beam hardening as more filtration was used. Data was obtained from simulations performed using Geant4 and for $10^8$ source particles. Data was re-binned in groups of five to create this figure.

$\pm 1.1\%$, maximum organ $= 2.7\%$. After normalization, the increase in relative organ dose due to the 3 mm stainless steel shelf backscatter was shown to be 0.12\% averaged over all organs for filter B [minimum organ $= -0.1\%$, maximum organ $= 0.4\%$]. Thus, the effects of backscatter due to the inclusion of the 3 mm steel shelf had a negligible (<0.4\%) effect on the relative organ doses, and all results presented here in the following chapter will report dose values from simulations and physical measurements with the steel shelf removed.

Moreover, the physical ion chamber measurements confirmed a slight increase ($6.4\% \pm 2\%$ for filter B) in measured dose due to the inclusion of the 3 mm stainless steel shelf on the XRAD-320. The Monte Carlo study looking at dose increase to a $1 \times 1 \times 1 \ \text{cm}^3$ water volume reported a $3.47\% \pm 0.01\%$ dose increase for filter B, and
4.31% ± 0.01% dose increase for filter C, when the 3 mm stainless shelf was added to the simulation model.

Dose distributions in a cross section of the 33 g MOBY mouse phantom are shown in Figure 5.5. Soft tissue structures had approximately uniform absorbed dose within this cross plane, but skeletal tissue showed substantially increased dose. The stomach contents, cerebrospinal fluid (CSF), lung airways, and colon content doses are not displayed (white) since the contents of these organs are generally not of radiological concern.

Simulation organ dose results for the three MOBY mouse phantom sizes and the three filter types are shown in Figure 5.6. Firstly, in soft tissue of the 33 g mouse,
Figure 5.5: Dose distribution in the central coronal slice of the 33 g MOBY mouse phantom for (a) filter A, (b) filter B, and (c) filter C. Reported doses were normalized per $1 \times 10^9$ source particle histories (emitted photons from x-ray tube).

The ratio of the largest to the smallest relative organ dose was 1.34, 1.30, and 1.26 for filters A, B, and C, respectively. Secondly, in soft tissue of the 23 g mouse, the ratio of the largest to the smallest relative organ dose was 1.34, 1.29, and 1.24 for filters A, B, and C, respectively. Lastly, in soft tissue of the 12 g mouse, the ratio of the largest to the smallest relative organ dose was 1.32, 1.27, and 1.23 for filters A, B, and C, respectively.
Figure 5.6: Relative organ dose values obtained from Monte Carlo simulation results in MOBY mouse phantom for three different (filter A, B, C) x-ray spectra produced from the XRAD-320. Relative dose values were found to be nearly independent of the mouse size within the range of sizes studied: (a) 12 g, (b) 23 g, and (c) 33 g. Doses shown here were normalized to the maximum organ dose, found to occur in skeletal mineral bone tissue.
5.4 Discussion

For the HVL measurements, ideal agreement among the physical and the Monte Carlo data would result in a measured dose value of 0.5 relative to the initial unattenuated value for the equivalent thickness (1 HVL) of copper material added. The resulting Monte Carlo x-ray spectra were found to be slightly softer than the experimentally measured beams, suggesting that the organ dose values reported here may be representative of x-ray beams of slightly lower filtration. However, the HVL does not uniquely characterize an x-ray beam; two separate x-ray spectra may have the same HVL, but different overall energy spectra.

Reiterating, the dose tables presented here are not meant to be used as a lookup table for x-ray irradiator users to prescribe dose to mice. Rather, the results presented here are meant to demonstrate the magnitude of dose errors that result from failing to account for filter specific, and organ specific dose rates when prescribing dose to mice. In addition, the range of organ doses offer insight into the heterogeneity of the dose distribution within a mouse for a whole-body irradiation setup using orthovoltage x-rays. A physicist should be consulted to determine the dose rate table specific to the users’ irradiation geometry and setup. The resulting dose errors from using the conventional dose prescription method (based on a single point dose measurement, and assuming homogeneous dose throughout mouse) are displayed in Table 5.3.

The dose distribution for filter A was more inhomogeneous than the dose distributions from the more highly filtered spectra (such as filter C), due the greater degree of attenuation with increasing depth and beam hardening in tissue. When considering normalization to the liver, increasing the filtration from filter A to filter C was shown to increase the soft-tissue organ dose percent difference range from 32% to 25% for the 33 g mouse, 32% to 23% for the 23 g mouse, and 31% to 23% for the 12 g mouse. For the conventional dose prescription method that uses a single point
Table 5.3: Simulation results of the calculated dose prescription percent errors for comparing the resulting dose error in each organ if a uniform dose distribution is assumed according to the conventional dose prescription method. All dose errors are relative to the dose in the liver. Absolute standard error of the mean were all below ± 0.5%. For full list of standard error values, see (Belley et al., 2014).

<table>
<thead>
<tr>
<th>Mouse Size</th>
<th>12 g</th>
<th>23 g</th>
<th>33 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Gonads</td>
<td>-1.9 %</td>
<td>-1.9 %</td>
<td>-1.7 %</td>
</tr>
<tr>
<td>Bladder</td>
<td>-2.8 %</td>
<td>-2.2 %</td>
<td>-2.3 %</td>
</tr>
<tr>
<td>Liver</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Thyroid</td>
<td>-1.7 %</td>
<td>-0.8 %</td>
<td>-0.3 %</td>
</tr>
<tr>
<td>Bone</td>
<td>267.4 %</td>
<td>236.2 %</td>
<td>176.8 %</td>
</tr>
<tr>
<td>Brain</td>
<td>15.3 %</td>
<td>12.5 %</td>
<td>10.6 %</td>
</tr>
<tr>
<td>Red bone marrow</td>
<td>27.8 %</td>
<td>24.4 %</td>
<td>20.3 %</td>
</tr>
<tr>
<td>Colon</td>
<td>2.0 %</td>
<td>1.7 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>Lung</td>
<td>8.8 %</td>
<td>6.8 %</td>
<td>6.8 %</td>
</tr>
<tr>
<td>Stomach</td>
<td>9.3 %</td>
<td>7.3 %</td>
<td>6.6 %</td>
</tr>
<tr>
<td>Range (excluding bone)</td>
<td>31.0 %</td>
<td>27.0 %</td>
<td>23.0 %</td>
</tr>
</tbody>
</table>

dose measurement, a maximum of a 23%-32% error may result in the calculated organ dose value, depending on the filter choice, size of the mouse, and organ that is targeted.

The second highest organ dose (second to mineral bone) was shown to occur in the red bone marrow, and the third highest was in the brain. The gonads and the bladder were organs with the smallest relative dose difference compared to the liver. Differences in relative dose among these organs with the maximal and minimal doses could be most likely attributed to anatomical variation such as differences in proximity to mineral bone structure, and differences in attenuation effects owing to the organs depth from the beam entrance.

A new method of calibration is proposed, to accurately calculate the organ based dose rates in mice (Equation 5.2). This method utilizes a thermo-luminescent dosimeter (TLD) or a metal oxide semiconductor field effect transistor (MOSFET) to make a physical measurement in a rodent-morphic phantom (Figure 5.7), and then apply factors to correct to location and organ specific dose rates. The mouse phantom, made of tissue equivalent plastic, generates realistic scatter and attenuation for a
measurement that models the shape, size, and placement of the mice. By placing the dosimeter along the central axis via a drilled hole in the phantom, an in-tissue measurement is obtained as a reference dose. The next step in the method utilizes the relative organ doses calculated from Monte Carlo (similar to those shown in Figure 5.6, but normalized to the reference point instead of the bone dose) to scale the MOSFET reference dose for all other organ locations. When using this method, researchers can deliver radiation to animals based on a filter and organ specific dose rate prescription, allowing them to theoretically avoid the aforementioned dose errors associated with the conventional prescription method.

The new dose equation is given by:

\[
t_O = \frac{D_{T,O}}{D_{M,Ref} \times C_O}
\]  

(5.2)

Where \( t_O \) is the organ-specific calculated irradiation time, \( D_{T,O} \) is the target dose prescribed to a given organ, \( D_{M,Ref} \) is the filter specific measured dose rate at the reference point, and \( C_O \) is the organ and filter specific correction factor to scale the dose based on the MOBY mouse phantom relative organ dose values. For a target dose of \( D_{T,O} = 4 \) Gy to the lung of a 23 g mouse, with a measured dose rate of \( D_{M,Ref} = 1 \) Gy/min using filter B, and with a relative scaling factor of \( C_O = 1.082 \), the user would be advised to irradiate mice for a total of 3.7 min. Comparing this to the 4 min irradiation time computed using Equation 5.1 demonstrates that the conventional prescription method would have led to a dose higher than this by roughly 8%.

It should be noted that the XRAD-320 machine has been shown by others to have good beam uniformity (4.4% standard deviation) over the usable x-ray field (McGurk et al., 2012). However, since all Monte Carlo simulations and physical measurements reported here were performed in the center of a 20x20 cm\(^2\) x-ray field, animals should
also be centered in the x-ray field as this is most commonly the location where calibration was performed.

This study found that for all filters (A, B, and C) the dose to mineral bone was several times higher than the average dose to the soft-tissue organs. For a further discussion on the topic of x-ray dose enhancement in high-Z materials due to the photoelectric effect, see Chapter 6. To achieve a given target dose to mineral bone, the irradiation time would be a factor of approximately one-third of the value calculated using the conventional prescription method.

5.5 Conclusion

Monte Carlo simulation studies conducted on mouse phantoms demonstrated that the conventional dose prescription method may lead to large errors in calculated organ doses. Likewise, these results suggest that organ dose errors may be minimized by calibrating the dose rates for all filters, and using different dose rates for different organs. Lastly, findings suggest that more uniform doses throughout all soft tissue
organs can be achieved by using more highly filtered orthovoltage x-ray beams.
Monte Carlo, Red Bone Marrow Dose

This chapter is devoted to the study of calculating the absorbed dose to red bone marrow (RBM) in mice, using high resolution Monte Carlo studies and anatomically accurate virtual phantoms derived from micron-resolution CT-images. The study considers both isotope type \(^{137}\text{Cs}\) gamma-irradiators and orthovoltage irradiators operated at 320 kV and 160 kV. An estimation of the spatial dose gradients within the bone marrow (BM) compartments are analyzed in relation to the x-ray beam quality. In addition to Monte Carlo simulations, in-vivo and ex-vivo experiments were carried out using cell survival of hematopoietic progenitors to study the realistic consequences of x-ray irradiation relative to \(^{137}\text{Cs}\), and to validate the simulations.

6.1 Introduction

Radiological disasters and clinical radiation therapy treatments in humans often involve high energy radiation; such as gamma-ray producing isotopes (iodine, cesium, or cobalt) or megavoltage (MV) linear accelerators capable of electron and photon production in excess of 18 MeV. Accordingly, small animal radiation biology studies (pharmaceutical development and radiation therapy treatment design) used as a
preclinical model for these events should accurately represent the effects due to high energy radiation.

Traditional radioisotope based small animal irradiators are being phased out in favor of x-ray irradiators that pose fewer risks to national security (Dodd and Vetter, 2009). A scientific understanding of the differences in dose absorption and relative biological effect (RBE) between these two different irradiator types is essential to assess validity and for comparison of results.

Early findings of increased lethality to mice due to orthovoltage irradiations prompted studies to characterize dose and RBE for photon irradiation in the BM compartment of mice and humans for MV photons, kV photons, and isotope based gamma irradiation (Shalek et al., 1962; Epp et al., 1959; Gengozian et al., 1986; Sinclair and Blackwell, 1962). Studies have provided estimates of dose to BM using ex-vivo models with dosimetry materials in place of the BM, such as the use of human cadaver trabecular bone filled with LiF powder (King and Spiers, 1985), or the use of porous Pyrex glass (bone equivalent) filled with ferrous sulphate (Ellis, 1966).

The majority of the active red BM resides in trabecular bone structures; iron uptake studies have shown a large fraction of the BM to reside in the spine (32.6%), as compared to the extremities (27.8%) such as the femur (6.7%) (Boggs, 1984). Further, others have used progenitor assays to show that when harvesting cells via crushing with a mortar and pestle, the spine was responsible for 52% of the total marrow cellularity harvested from the entire skeleton, with the skull (11%) and femurs (10%) representing the next most abundant marrow spaces (Colvin et al., 2004). Dosimetry within the compartments of both the spine bones and femurs warrants careful study because they are important sources of active BM and popular choices when harvesting BM from mice.

The average dose to a macroscopic collection of bone marrow (within a relatively similar location such as the femur) may be estimated by:
\[ \bar{D} = \int P(x)D(x)dx \] (6.1)

Where \( \bar{D} \) is the average dose, \( P(x) \) is the fraction of BM at a given distance \( x \), and \( D(x) \) is the dose to BM at a given distance \( x \).

6.2 Methods and Materials

6.2.1 Digital Virtual Phantoms

A whole-body x-ray CT was performed on one mouse at MIT using a GE eXplore CT120 machine (GE Medical Systems). Acquisition used 80 kV, 32 mA, and a full 360-degree rotation yielding 1200 views. Images were reconstructed with isotropic voxels of 25 \( \mu m \) resolution. This whole body CT image data-set was used to localize the anatomy and locations of the vertebra and femur within the mouse.

After this 25 \( \mu m \) resolution whole-body CT was performed, both the (i) lumbar vertebrae (L2 through L5) and the (ii) left femur were excised from the mouse and immersed in ethanol for fixation. These extracted bones were then shipped to SCANCO Medical AG (Bruettisellen, Switzerland) for CT scanning at a resolution of 1 \( \mu m \). These high resolution scans were acquired on a \( \mu \)CT 50 scanner, via a 5 \( \mu m \) focal spot size at 70 kV and 86 mA.

The SCANCO CT images provided 3 datasets:

- Vertebra, 1 \( \mu m \) resolution, 4200x4200x5000 voxels.
- Femur (Partial FOV), 1 \( \mu m \) resolution, 3400x3400x5000 voxels.
- Femur (Full FOV), 5 \( \mu m \) resolution, 1000x1000x3200 voxels.

Planar x-ray radiographic images (scouts) from the SCANCO CT acquisition are shown in Figure 6.1.
A threshold was applied to the SCANCO acquired CT images to define the mineral bone structures in accordance with the Hounsfield Unit values of the voxels. Since the ethanol present outside of the bone was found to have similar Hounsfield Unit values as the BM regions (Figure 6.2), the use of a simple second mask to define the BM was not possible. Thus, ITK-SNAP software (Yushkevich et al., 2006) was used to contour the outer surface of the bone structure. This contoured region was set to a binary value of “1” and was multiplied with the mineral bone mask set as a value of “0”. The resulting images after the multiplication used a value of “1” for regions inside the mineral bone, providing a definition of the anatomic regions corresponding to the BM compartment.

The final phantoms constructed from the CT images (Figure 6.3) defined three regions: bone, BM, and other. These phantoms were placed as daughter volumes in a 2.5 cm diameter cylinder of water representative of the rest of the mouse. The femur and vertebra daughter volume locations were positioned within this parent volume to represent realistic anatomical positions as measured from the 25 µm resolution
Figure 6.2: Axial images from the 1 \( \mu m \) resolution SCANCO CT scans of the (a) femur and (b) vertebra. Since the bones were stored in ethanol prior to scanning, the trabeculae had to be contoured to define regions of the anatomy that contained BM. Note - images not shown to scale.

Whole body CT images acquired on the eXplore CT120. Thus, all regions other than the bone and BM in the phantoms were set to water material in the simulations. The computer used for simulations had 64 GB available random access memory (RAM), requiring the final phantom voxel size to be down-sampled to 5 \( \mu m \) resolution, due to the memory requirements of the GATE simulations and the limitation in the total number of voxels that defined the phantom geometry due to the use of 32-bit data-types for voxel indexing in the GATE source code.

6.2.2 Distance Calculation

The primary goal of this experiment was to obtain a relationship of absorbed dose to the BM volume as a function of distance to the nearest mineral bone. Thus, the distance of each image voxel corresponding to BM material was calculated to the nearest image voxel corresponding to mineral bone. The two main challenges were (i) the large anatomy file size of the phantoms (femur was 0.9 GB as 8-bit data type, vertebra was 0.68 GB as 8-bit data type), (ii) the long computation time of the distance algorithm to seek out the nearest cortical bone structure in all 3-dimensions (was performed for each individual BM voxel).
The algorithm ultimately developed systematically went through the BM voxels one-by-one and searched for the nearest cortical bone voxel. This was achieved using a multi-step process:

1. Selected a voxel of BM material in the 3D phantom array with indices given by $[i_0, j_0, k_0]$.

2. Individually and systematically incremented a given index ($i_0 + 1$), until a voxel of mineral bone was found with indices given by $[i_0 + n, j_0, k_0]$.

3. Computed the linear distance ($\Delta_M$) according to the number of times the loop in step 2 was run (i.e: $\Delta_M = n$).

4. Compared the distance value ($\Delta_M$) to any previously computed distance values in the output distance array. If the distance value ($\Delta_M$) was a new minimum, store it in memory at position of $[i_0, j_0, k_0]$ in the output distance array.
5. Steps 2 through 4 were then repeated by decrementing the index \([i_0 - n, j_0, k_0]\), thus providing a search in the opposite direction.

6. Steps 2 through 5 were then repeated for subsequent axes, via searches along the \(j\) and \(k\) array index values.

7. Steps 2 through 6 were then repeated after rotating the 3D array in the x, y, and z axes; yielding a search at oblique angles such as at \(45^\circ\) and \(22.5^\circ\).

The resulting distance output files were 3D arrays with the same coordinate system as the input phantom anatomy, and with values corresponding to the distance of individual BM voxels to cortical bone (Figure 6.4). The output file sizes were 1.3 GB for the vertebra, 1.8 GB for the proximal femur phantom, and 0.89 GB for the distal femur phantom. Due to the nested loop structure of the algorithm, the computation took more than four hours to run, even when parallelized on four cores. Due to the long computation time, other existing algorithms were explored (e.g. grassfire transform algorithm), but these algorithms were not pursued since scaling them for use on 3-dimensional arrays would be a non-trivial task, and a successful outcome of a 3D implementation was not assured.

To overcome the slow computation time, a parallelized algorithm was developed using Python. This software was written to split up the image into four sets (known as “jobs”) of smaller work sizes, and to evenly distribute these parallel jobs to individual CPU processors. Additionally, job splitting was achieved while still maintaining a limited memory footprint, via a single shared instance of memory corresponding to the output data array of distance values. In doing so, the software was able to take advantage of a quad core Intel i7-3820 processor, which utilized each of the four cores for calculating the distance of approximately one quarter of the total BM voxels in the original phantom volume dataset.
Figure 6.4: (a) The three-region vertebra phantom of bone (white), BM (gray), and outside regions (black) created from the 1 µm SCANCO CT images. (b) Distance results displayed as a contour map, representative of the distance of each BM voxel to the nearest cortical bone structure computed according to software developed in Python.

6.2.3 Particle Transport Dose Simulations (Monte Carlo)

The GATE Monte Carlo toolkit (Jan et al., 2011, 2004; Strul et al., 2003) was used to score dose in the simulation study. The dosimetry studies were broken up into two parts: (i) a microdosimetry study performed on the SCANCO high resolution CT image sets, and (ii) a macrodosimetry study performed on the MOBY whole body mouse phantom. The purpose of these two studies were (i) to calculate the localized dose gradients within the skeletal structures of the femur and vertebra, and (ii) to assess the systemic whole body dose gradients throughout the entire mouse.

Microdosimetry - SCANCO Image Based Phantoms

As opposed to using either a spongiosa or a chord-based model, a full 3-D voxel based particle transport model was chosen. Full 3-D voxel based models have been shown to provide the most accurate and realistic dosimetry results (Shah et al., 2005b), with
the ability to account for tracking of non-linear electron trajectories at energies that exceed 50 keV (Shah et al., 2005a). As previously mentioned, memory requirements of the available computer used for the simulation were capped at 64 GB of random access memory (RAM). The original CT dataset of the vertebra had approximately $8.86 \times 10^{10}$ voxels, and as an 8-bit data-type this would correspond to a file size of more than 82 GiB. Further, the outputs of the GATE simulation store (i) dose and (ii) uncertainty statistics individually for each voxel as 32-bit floating point data-types, increasing the memory requirement by a factor of eight in relation to just the phantom file size itself. As a result, the dose simulation was performed on voxel based virtual computational phantoms at 5 $\mu$m resolution, and all dose results were stored with an equivalent resolution of 5 $\mu$m. Biologically speaking, 5 $\mu$m is roughly half the overall diameter of a hematopoietic stem cell, providing sufficient resolution to compute the dose gradients to a fraction of the HSC size (Spangrude et al., 1988).

From preliminary studies, BM voxels $>100$ $\mu$m distance to mineral bone were found to be beyond the extent of the dose gradient caused by photo-electron dose enhancement. Thus, 100 $\mu$m was selected as the equilibrium region of the BM, to which all other BM dose values (dose-enhancement) were compared against. All relative dose values reported to BM in this chapter will be in relation to the equilibrium BM dose at depths greater than 100 $\mu$m.

The material definitions used for the simulation were water for the 2.5 cm diameter parent volume representative of the mouse body, ICRU-44 “cortical bone” material (White et al., 1989) for the mineral bone structures, and “spleen” (Woodard and White, 1986) as a reliable estimate of the marrow tissue material. A 50 cm focal spot source to surface distance (SSD) was used, representative of the typical XRAD-320 (Precision X-ray Inc., North Branford, CT) irradiator geometry. The mouse was positioned so the x-rays entered on the dorsal side.

According to the aforementioned constraints imposed on the overall size of the
phantoms that could be simulated in GATE, the dosimetry was split up into three separate computations, requiring more modifications to the originally created phantoms by cropping the FOV according to: (i) distal femur (682 x 682 x 1001), (ii) proximal femur (918 x 632 x 1631), and the (iii) vertebra (842 x 842 x 1000).

The number of source particle histories used for the microdosimetry simulations was $10 \times 10^9$. The source spectra for the 320 kV irradiations were based on prior x-ray simulations performed in Geant4 and validated with physical HVL measurements (Belley et al., 2014). For the 160 kV irradiations, x-ray spectra were obtained from the software SpekCalc (Poludniowski et al., 2009). The photon spectra (Figure 6.5) used for the GATE dosimetry were representative of x-rays at the following tube potentials and HVL (kV/HVL (mm Cu)): 160/0.62, 320/1.0, and 320/4.0. In addition, dosimetry was performed using monoenergetic 662 keV photons, representative of $^{137}$Cs gamma irradiators. The irradiator beam parameters are summarized in Table 6.3.

The physics used in the simulations were selected to provide accurate, high resolution results for low-energy particle transport. As a starting point, the “Physics parameters for radiation therapy applications” guide was used to select the physics lists. A few minor changes were made to the recommended physics, such as the use of the Livermore physics lists (photoelectric, Compton, and Raleigh models) as well as 0.001 mm cut values for secondary particle tracking. All physics processes used in the simulations are summarized in Table 6.1.

**Macrodosimetry - MOBY Mouse Phantom**

Additional particle transport simulations were performed on the realistic voxel based MOBY mouse phantom (Segars et al., 2004) at the macroscopic level. The purpose

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Figure 6.5: X-ray spectra used for the dosimetry simulations. Three distinct beam qualities were studied, with varying levels of filtration. All utilized a tungsten anode material. The 320 kV beams were obtained using Geant4 based on XRAD-320 geometry, and the 160 kV beam was obtained using SpekCalc. The area under the curves were normalized for display purposes.

of these simulations was to characterize the whole body dose distribution relative to differences in x-ray tube beam qualities, and in comparison to gamma irradiations via $^{137}\text{Cs}$. Using an entire mouse phantom provided insights into differences in attenuation, beam hardening, and scatter. The MOBY model was chosen to represent a 23 g mouse, with $0.1286 \times 0.1286 \times 0.1286$ mm$^3$ voxels. The physics used for the GATE simulation are summarized in Table 6.1. Similar to the microdosimetry studies, 50 cm SSD was used to model the XRAD-320 geometry. A total of $1 \times 10^9$ source particle histories were simulated, and doses were stored again using the dose actors provided in GATE. The MOBY phantom did not include trabecular modeling; the bones consisted of hollow cavities and the BM regions could be modeled with the material of the user’s choice. Here, the hollow cavity material was modeled using “spleen” material in the same manner as in the microdosimetry simulations. This
was chosen for consistency, and to show limitations of the MOBY mouse phantom for accurate modeling of the BM compartments. Further, use of a soft tissue material for modeling the trabecular spaces provided a conservative estimate of the dose enhancements, as others have shown this method to provide the lower limit to the dose enhancement experienced by the bone marrow as compared to a homogeneous mixture of mineral bone and soft tissue known as “spongiosa” (Lee et al., 2006b; Johnson et al., 2011). The average dose in all organs was compared to the average dose to the liver, chosen because the liver is a centrally located and large soft tissue organ.

Table 6.1: Physics lists used for the Monte Carlo particle transport simulations.

<table>
<thead>
<tr>
<th>Microdosimetry Setting</th>
<th>Macrodosimetry Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monte Carlo Toolkit</td>
<td>GATE v6.1</td>
</tr>
<tr>
<td>Number Primaries</td>
<td>$10 \times 10^9$</td>
</tr>
<tr>
<td>Photoelectric Model</td>
<td>Livermore</td>
</tr>
<tr>
<td>Compton Model</td>
<td>Livermore</td>
</tr>
<tr>
<td>Raleigh Model</td>
<td>Livermore</td>
</tr>
<tr>
<td>e- e+ Multiple Scattering</td>
<td>Urban93</td>
</tr>
<tr>
<td>Electron Ionization</td>
<td>Standard</td>
</tr>
<tr>
<td>dE/dx Table Binning</td>
<td>220</td>
</tr>
<tr>
<td>Lambda Table Binning</td>
<td>220</td>
</tr>
<tr>
<td>Cuts</td>
<td>0.001 mm</td>
</tr>
<tr>
<td>e- e+ Multiple Scattering</td>
<td>fUseDistanceToBoundary</td>
</tr>
<tr>
<td></td>
<td>fUseDistanceToBoundary</td>
</tr>
<tr>
<td>Step Limit Type</td>
<td>0.2 / 0.1 mm</td>
</tr>
<tr>
<td>Step Function (dRR/fR)</td>
<td>0.2 / 0.1 mm</td>
</tr>
</tbody>
</table>

6.2.4 Dose Analysis

Dose Output Format

The GATE simulations were setup to provide three different output files. These output files were all separate dose actors for the following three quantities: (i) dose in each voxel, (ii) dose uncertainty in each voxel, and (iii) dose squared in each voxel. Quantity (iii) was necessary for propagating the uncertainty for subsets of voxels,
according to the uncertainty equation defined in the GATE “Users Guide”.2

The femur was subdivided into the distinct regions of the metaphysis and diaphysis as shown in Figure 6.1A (Ellis et al., 2011). Division into these regions yielded separate dose estimates for the trabecular rich regions at the ends of the femur (proximal and distal metaphysis) in comparison to the trabecular poor (and RBM poor) regions of the diaphysis.

PDD Analysis

The macrodosimetry simulations performed on the MOBY mouse phantom were used to calculate percent depth dose (PDD) profiles. The PDD profile takes into account normalized dose due to increasing attenuation and distance from the x-ray tube. To calculate the PDD, the depth was calculated along the dorsal-ventral axis to the point of the phantom where the photon beam was incident, and the dose to all soft tissue voxels at a given depth was averaged in to a single data point. In total, five different radiation beams and geometries were simulated for the PDD data: the three x-ray beams used in the microdosimetry study, as well as two 137Cs beams (one which incorporated a 5 mm thick piece of acrylic material to simulate the mouse container used during the gamma irradiation (Figure 6.6)). The 5 mm acrylic piece was included to study the effects of buildup, due to the theorized effect of the 662 keV monoenergetic gamma rays achieving charged-particle-equilibrium at non-zero depth in soft tissue.

6.2.5 Physical Dosimetry

Physical dosimetry was performed on both the XRAD-320 irradiator and the Shepherd gamma irradiator (Mark I-68A, JL Shepherd and Associates, San Fernando, CA) to calculate the amount of time that all cell and mouse specimens should be

2 http://www.opengatecollaboration.org/UsersGuide
irradiated to achieve a dose of 6 Gy. Similarly, the dosimetry was used to set the machine mA values on the XRAD-320 to keep equivalent dose rates for both x-ray type and gamma type irradiations. Measurements on the XRAD-320 were for 320 kV tube potential, and with filters of [2.0 mm Al] and [1.50 mm Al + 0.25 mm Cu + 0.80 mm Sn] that produced beams with HVL of 1 and 4 mm Cu, respectively (Belley et al., 2014).

A combination of TLD (TLD-100, Harshaw Chemical Company, Solon, OH), radiochromic film (Gafchromic EBT2, International Specialty Products, Wayne, NH), and ion chamber (Radcal, Monrovia, CA) measurements were performed for full characterization of the dose rates in all beams. The lowest dose rate condition was for the 4 mm Cu HVL beam on the XRAD-320. To obtain equivalent dose rates for this condition in comparison to the highest dose rate condition (Shepherd gamma irradiator), decreased dose rate on the gamma irradiator was achieved by adding lead shielding (Figure 6.8), and increased dose rate on the XRAD-320 was achieved by
using Styrofoam blocks to decrease the SSD from the standard shelf height of 50 cm. The 1 mm Cu HVL beam on the XRAD-320 was set to an equivalent dose rate as the gamma irradiator by careful selection of an appropriate mA value. Thus, the ex-vivo (cell) irradiations obtained a dose rate of approximately 100 cGy/min across all irradiator types and for all conditions. Similarly, for the in-vivo (mice) experiment, due to a difference in geometry caused by the container on the gamma irradiator, a dose rate of approximately 140 cGy/min could be achieved for all irradiations. The irradiation geometry is summarized in Table 6.2.

Table 6.2: Experimental radiation conditions used for the in-vivo and the in-vitro studies on the x-ray and gamma type irradiators.

<table>
<thead>
<tr>
<th>Irradiator</th>
<th>Filter</th>
<th>HVL (mm Cu)</th>
<th>E̅ (keV)</th>
<th>SSD (cm)</th>
<th>Tube Current (mA)</th>
<th>Dose Rate (cGy/min)</th>
<th>Tube Current (mA)</th>
<th>Dose Rate (cGy/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRAD-320</td>
<td>2.0 mm Al</td>
<td>1</td>
<td>85</td>
<td>60</td>
<td>6</td>
<td>95</td>
<td>10</td>
<td>145</td>
</tr>
<tr>
<td>XRAD-320</td>
<td>1.5 mm Al</td>
<td>4</td>
<td>150</td>
<td>35</td>
<td>7</td>
<td>108</td>
<td>9</td>
<td>143</td>
</tr>
<tr>
<td>XRAD-320</td>
<td>0.25 mm Cu 0.8 mm Sn</td>
<td>4</td>
<td>150</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>XRAD-320</td>
<td>1.5 mm Al 0.25 mm Cu 0.8 mm Sn</td>
<td>-</td>
<td>662</td>
<td>20</td>
<td>-</td>
<td>103</td>
<td>-</td>
<td>139</td>
</tr>
</tbody>
</table>

It should be noted that to best mimic the current methods of small animal irradiation, no attempt was made to correct for attenuation, scatter, or the effect of tissue inhomogeneities. All exposures, for both mice and cells, were based on a calculated time found using Equation 5.1. The measured dose rates were found using exposed TLD’s, specific for each individual beam quality. To accurately model the in-vivo experimental setup, the TLD’s were placed in the acrylic mouse containers used for all irradiations, and at the same location as the mice were planned to be irradiated at (along the central axis for XRAD-320, and in the rotating carousel container on the Shepherd gamma irradiator).

As previously mentioned, the dose rate of the Shepherd gamma irradiator was reduced to match the range of achievable dose rates on the XRAD-320. This was
accomplished by adding 0.79 cm of lead next to the source on the Shepherd irradiator. TLDs were calibrated in an open-field, free-in-air geometry setup, using a 6 cm$^3$ NIST traceable ion chamber for cross calibration to air-kerma. The TLD chips and ion chamber were placed on an acrylic holder to position all of the dosimeters side-by-side for a single-shot measurement (Figure 6.7). Using this method, the nC response of each individual TLD was directly compared to the ion chamber exposure measurement, and corrected back to dose using the appropriate f-factor for the given beam quality. F-factors were computed at the average energy of each of the three x-ray beam qualities, providing dose to soft tissue values. For the in-vivo setups, TLDs were sandwiched between two pieces of 9.4 mm thick bolus (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY) to mimic deep tissue dose as encountered by a mouse sized object. In addition, this bolus provided “build-up” for the Shepherd gamma irradiator experiments. TLDs were placed in the geometry representative of the mouse irradiation conditions, accounting for realistic conditions and attenuation encountered from the mouse holders. The TLDs were used to measure the dose rate for each beam quality, and later were used to correct back to the 6 Gy prescription dose.

Radiochromic film was calibrated at five individual dose levels using an exponential fit of exposure, measured using an ion chamber, to obtain a calibration curve of change in optical density vs. radiation quantity. The film was used to measure the x-ray field uniformity on the XRAD-320 specifically for the 35 cm SSD condition used for the 4 mm Cu HVL beam. Due to the reduced SSD, the field size was 14 x 14 cm$^2$ as compared to the standard 20 x 20 cm$^2$ field size when an SSD of 50 cm was used by placing samples on the steel shelf. To maintain uniform dose distributions along the x-ray field, mouse specimens were placed with the head-tail axis oriented perpendicular along the anode-cathode axis of the x-ray tube to negate the heel effect.
Figure 6.7: Calibration setup, using acrylic holder to position a batch of TLD-100 chips around a 6 cm$^3$ ion chamber. Chips were irradiated using 320 kV tube potential provided by the XRAD-320, at two distinct beam qualities of 1 mm Cu and 4 mm Cu HVL.

6.2.6 Ex-Vivo Animal Studies

To model cortical bone, a bone equivalent material (BEM, $\rho = 1.91$ g/cm$^3$) made of plastic (product code CB-19F2, CIRS Inc., Norfolk, VA) was placed in the bottom of one well plate for each irradiation condition. The dimensions of the BEM were 15 mm diameter, and 1.3 mm thick. For each beam quality, cells were placed in the 24-well plates in two locations: (i) in an empty well, and (ii) directly on top of the BEM. These cells were harvested from the lumbar vertebrae of a single male C57BL/6 mouse. The cell suspension was $2 \times 10^6$ cells in 1 mL of phosphate buffered saline with 2% fetal bovine serum. The entire plate setup was irradiated at a dose rate of approximately 1.0 Gy/min to a prescription dose of 6 Gy for x-rays at beam qualities of 1 and 4 mm Cu HVL (Figure 6.8), as well as on the $^{137}$Cs gamma irradiator (Figure 6.9).
Figure 6.8: Cell plates were located on the floor of the $^{137}$Cs irradiator. The grid pattern was used to map out the dose rates as a function of distance from the source. The sheets of lead (visible in the back) provided attenuation of the gamma rays to achieve a lower dose rate. The cell plates were placed on the floor of the irradiator to obtain oblique angles of radiation through the bone equivalent material.

6.2.7 In-Vivo Animal Studies

Male C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were used for the in-vivo radiation studies. They were three months of age and were all group housed in a pathogen free facility with 12:12 hour light/dark cycles, and with water and food provided ad libitum. Experiments were performed with approval from the institutional animal care and use committee (IACUC).

20 mice were used for the in-vivo studies, divided in groups of five mice, providing four mice for each irradiation condition. A single dose of 6 Gy was prescribed for each mouse, delivered using a whole-body treatment field to the un-anesthetized mice. For x-ray, the mice were irradiated in custom made acrylic boxes (7.75 x 3.30 x 2.80 cm
with wall thickness of 2.38 mm) that limited movement of the mice and prevented standing. For $^{137}$Cs gamma irradiation a cylindrical container was used to position the mice at the same height that the source was raised to during irradiation, and to allow for rotation during the treatment. The dose rates and SSD values of the beams were as follows: 320 kV 1 mm Cu HVL at 1.45 Gy/min and at an SSD of 60 cm, 320 kV 4 mm Cu HVL at 1.43 Gy/min and at an SSD of 35 cm, 320 kV 4 mm Cu HVL at 0.56 Gy/min at 60 cm, and $^{137}$Cs at 1.39 Gy/min (from 0.79 cm lead attenuation).
6.2.8 Clonogenic Survival

Cell survival from both the in-vivo and the in-vitro experiments was assessed using clonogenic survival of the hematopoietic progenitors from the harvested BM.

6.3 Results

The Python program developed to calculate the distance of the BM voxels to the nearest cortical bone structure was used on all of the digital virtual phantom datasets. The results were binned to create a histogram for each separate phantom and are shown in Figure 6.10. The trabecular rich regions of anatomy showed a substantially higher proportion of fractional volume of BM within close distance to bone. For the vertebra, 9% of the BM volume was within 5 \( \mu m \) distance to bone, representing the highest fractional volume for all anatomical regions. In contrast to this, the trabecular poor femur diaphysis had only \( \approx 3\% \) fractional volume of BM within 5 \( \mu m \) of bone.

6.3.1 Particle Transport Dose Simulations (Monte Carlo)

The percent depth dose (PDD) curves (Figure 6.11) show the combined effect of attenuation in tissue and reduced dose rate due to increased distance from the x-ray tube focal spot. This figure alone should convince the reader that a homogeneous dose distribution may not be achieved for the irradiation of a mouse specimen, even for the highest energy (662 keV from \(^{137}\text{Cs}\)) case. Comparing all of the PDD values at the 2 cm depth point, supports the finding that \(^{137}\text{Cs}\) had the least attenuation (85\% PDD) in comparison to the 0.62 mm Cu HVL beam at 160 kV (69\%), 1 mm Cu HVL beam at 320 kV (66\%), and 4 mm Cu HVL beam at 320 kV (71\%). Thus, the orthovoltage x-ray beams were all found to exhibit greater attenuation in the MOBY phantom, leading to substantially lower doses on the dorsal side of the MOBY phantom at the beam exit.
Figure 6.10: Histograms of bone marrow distance to cortical bone for different anatomical locations within mouse bones. Distances were calculated using an algorithm developed in Python, and all data was processed based on the anatomy of the digital virtual phantoms created from the 1 \( \mu m \) resolution CT images from SCANCO. This dataset represents \( P(x) \) from Equation 6.1.

The 100% PDD value occurred at 2.19 mm depth for \(^{137}\text{Cs} \) with no buildup, and at 1.80 mm depth for \(^{137}\text{Cs} \) when the acrylic buildup was used in the simulation (Figure 6.11B). Despite the decrease in depth to the point at which the maximum dose was achieved, the use of buildup had negligible effect on the PDD values at depths beyond 3 mm, after which the two PDD profiles tracked similarly throughout the remaining tissue. For the x-ray beams, the buildup depth to max PDD occurred at shallower depths of 0.64 mm, 0.26 mm, and 0.90 mm for the 0.62 mm Cu HVL beam at 160 kV, 1 mm Cu HVL beam at 320 kV, and 4 mm Cu HVL beam at 320 kV, respectively. The lower HVL beam quality (160 kV, 0.62 mm Cu HVL) achieved a maximum PDD value at a depth greater than the 320 kV beam at 1 mm Cu HVL; an effect that may be explained by the smaller proportion of low energy photons (below 45 keV) in the 160 kV beam.
Figure 6.11: Percent depth dose plots in the MOBY mouse phantom for different x-ray beam qualities on orthovoltage irradiators and for $^{137}$Cs gamma irradiation. (a) Displays full depth dose curves and (b) shows the first 3 mm of data to highlight the differences in buildup at shallow depths for the $^{137}$Cs beams with and without buildup material.

Macrodosimetry - Absorbed Dose, to Whole MOBY Skeleton

The MOBY mouse phantom provided previously segmented organ definitions, and enabled the systemic absorbed dose to the skeleton (Figure 6.12) and the bone marrow to be tabulated. As previously mentioned, dose calculations to the bone marrow found using the MOBY mouse were underestimated due to the lack of trabecular modeling and the use of spleen material for the modeling of the BM, and will represent the lower limit to the dose enhancement (Johnson et al., 2011). When normalized to the average dose to the liver, the average normalized dose absorption throughout the entire MOBY BM was calculated to be 1.22, 1.19, 1.17, and 1.06 for the photon beam qualities of 0.62 mm Cu at 160 kV, 1 mm Cu HVL at 320 kV, and 4 mm Cu HVL at 320 kv, and $^{137}$Cs, respectively. These doses to the BM found using the MOBY phantom will be discussed here only as a tool to compare the relative effect of the differences in beam energy among the x-ray and $^{137}$Cs irradiators. Additionally, though it requires further work, the BM doses calculated from the MOBY phantom
may in effect provide an estimate of the “Equilibrium Dose” (>100 µm from cortical bone) to the BM. If this is true, future work may seek to use the MOBY phantom to calculate the equilibrium BM doses, and then utilize the microdosimetry results to correct for the trabecular modeling within the BM compartment.

**Figure 6.12**: (a) Rendered image of the skeletal anatomy using the 25 µm resolution CT dataset from the C57BL/6 mouse in which the lumbar vertebrae and femur were harvested from (highlighted in red). (b) Heat map of the dose distribution throughout the MOBY mouse whole body phantom from x-ray irradiation at 320 kV, 1 mm Cu HVL. Output from Monte Carlo simulation of $1 \times 10^9$ source particle histories, rendered into a 3D view using the AMIDE VolPack volume rendering library (shear-warp factorization technique).

Likewise, when normalized to the average dose to the liver, the average normalized dose absorption to the mineral bone was 3.79, 3.62, 2.99, and 0.95 for the photon beam qualities of 0.62 mm Cu at 160 kV, 1 mm Cu HVL at 320 kV, and 4 mm Cu HVL at 320 kv, and $^{137}$Cs, respectively. These values calculated here match up well with previously reported values in the literature, in which a factor of three to five times higher dose absorption to bone relative to soft tissue was shown for 100 kV
and 225 kV beams in a mouse (Chow et al., 2010). The use of the acrylic buildup material for $^{137}$Cs had no effect in comparison to a $^{137}$Cs beam with no buildup, when considering the ratio of the dose to soft tissue for both the bone marrow (1.06) and the mineral bone (0.95).

*Microdosimetry - Absorbed Dose to the Bone Marrow Compartment*

Throughout the entire bone marrow compartment of both the femur and the vertebra, the absorbed radiation dose was binned as a function of distance (5 $\mu$m distance bins) and plotted as shown in Figure 6.14 and Figure 6.15. The dose enhancement was most substantial for distances to mineral bone of less than 60 $\mu$m, and for the lower energy x-ray beams.

Noting that these plots of distance vs. dose do not take into account the fractional volume of bone marrow that resided at these distances (Figure 6.10), values of the average increase to the entire BM volume of the vertebra were calculated and were found to be 31%, 17%, 8%, and 1% for 0.62 mm Cu HVL at 160 kV, 1 mm Cu HVL at 320 kV, 4 mm Cu HVL at 320 kV, and $^{137}$Cs, respectively, shown in Table 6.3. Thus, the combined effects of the (i) dose gradient (Figure 6.14 and Figure 6.15) and the (ii) fractional volume of bone marrow (Figure 6.10) play an important part in the overall dose to the BM (Equation 6.1).

The highest dose enhancement in the BM compartment was for the lowest effective energy beams (Figure 6.13), with the high energy gamma radiation of $^{137}$Cs producing the least dose enhancement. The dose enhancement was similar for the vertebra in comparison to the metaphysis of the femur, as expected due to the similarity of the anatomical structure depicted from the bone marrow distance histogram shown in Figure 6.10. The trabecular poor diaphysis of the femur showed substantially reduced dose enhancement to the bone marrow. The dose enhancement of up to 31% averaged over the BM volume in trabecular rich regions of the murine
anatomy was consistent with findings published by others relating to dose enhancement in active marrow for humans, with reported enhancements of 25-30% attributed to photon irradiations of 50 keV (Johnson et al., 2011).

Table 6.3: Monte Carlo parameters and microdosimetry results for the 5 \( \mu m \) digital virtual phantoms of the femur and vertebra.

<table>
<thead>
<tr>
<th>Monte Carlo Parameters</th>
<th>Average Dose Ratio to BM vs. Equilibrium BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>( kV )</td>
<td>Added Filtration</td>
</tr>
<tr>
<td>160</td>
<td>0.3 mm Cu</td>
</tr>
<tr>
<td>320</td>
<td>2.0 mm Al</td>
</tr>
<tr>
<td>320</td>
<td>1.5 mm Al</td>
</tr>
<tr>
<td>137Cs</td>
<td>0.25 mm Cu</td>
</tr>
</tbody>
</table>

Table 6.4 summarizes the absolute dose results from the Monte Carlo studies calculated to the “equilibrium BM”, defined to be the regions of BM at distances greater than 100 \( \mu m \) from mineral bone. Concerning the absolute dose values to the equilibrium BM, a higher dose was found to occur in the vertebra as compared to the femur. The ratio of the equilibrium BM dose to the vertebra relative to the femur was found to be 1.24, 1.25, 1.15, and 1.10 for 0.62 mm Cu HVL at 160 kV, 1 mm Cu HVL at 320 kV, 4 mm Cu HVL at 320 kV, and the \(^{137}\text{Cs}\) beams, respectively. It should be highlighted, that despite the similarities in the PDD profile of the 0.62 mm Cu HVL beam in comparison to the 4 mm Cu HVL beam (Figure 6.11), a substantial difference (1.24 vs 1.15) was found in the equilibrium dose ratio between these two anatomical locations, respectively. Thus, the PDD profile in soft tissue alone does not tell the whole story to understand dose to BM at different anatomical locations within the mouse, as beam hardening effects and the relative ratio of low energy photon components may play a role. Further, the less-steep dose gradients within the BM compartment associated with the higher energy beam (4 mm Cu HVL) may also have an effect.
Figure 6.13: Histogram of the Monte Carlo microdosimetry data displaying the volume of BM receiving a given dose ratio for different photon beam energies. Dose ratio was defined here as the ratio of the dose to the BM relative to the dose to the BM at distances greater than 100 \( \mu m \) from mineral bone. Figure legends display the average value over the entire BM compartment. Separate anatomical regions were analyzed according to the (A) diaphysis of the femur, (B) distal metaphysis of the femur, and (C) vertebra.
Figure 6.14: Microdosimetry Monte Carlo results analyzed to display relation of the relative bone marrow dose as a function of the distance from mineral bone. Two separate regions of the femur were separately analyzed to assess effects of anatomy on the BM dose. Overall, similar dose gradients were found to occur in both the diaphysis and the metaphysis of the femur. The reader is reminded that the fractional volume of bone marrow at a given distance from bone is drastically different in these two regions, leading to large differences in the overall dose absorbed. This dataset represents \( D(x) \) from Equation 6.1.

Table 6.4: Microdosimetry results of the absolute dose values to the BM.

<table>
<thead>
<tr>
<th>Digital Virtual Phantom</th>
<th>Absolute Dose (Gy) to Equilibrium BM (&gt; 100 micron depth)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.62 mm Cu HVL</td>
</tr>
<tr>
<td>Femur</td>
<td>(2.7 \times 10^{-4})</td>
</tr>
<tr>
<td>Proximal Metaphysis</td>
<td>(2.6 \times 10^{-5})</td>
</tr>
<tr>
<td>Diaphysis</td>
<td>(2.7 \times 10^{-5})</td>
</tr>
<tr>
<td>Distal Metaphysis</td>
<td>(3.3 \times 10^{-5})</td>
</tr>
<tr>
<td>Vertebra</td>
<td>(3.3 \times 10^{-5})</td>
</tr>
<tr>
<td>Ratio (Vertebra/Femur)</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Figure 6.15: Additional depth-dose data plots for the vertebra and distal metaphysis of the femur. Results are similar to those shown in Figure 6.14. This dataset represents $D(x)$ from Equation 6.1.

6.3.2 Clonogenic Survival Studies

Increased cell killing with decreasing photon energy was observed in the hematopoietic progenitor cell populations of the bone marrow. For the in-vitro study, 6 Gy dose to the plated BM cells yielded a 1% survival rate as observed by clonogenic assay. When the cells were plated on the BEM, the lowest energy radiation (1 mm Cu HVL) was found to produce a statistically significant ($p < 0.013$) increase in cell killing relevant to the non BEM study (Figure 6.16); whereas statistically significant cell killing was not observed between these two conditions for either of the higher energy beams (4 mm Cu HVL x-ray, and $^{137}$Cs).

For the in-vivo studies, a statistically significant increase in cell killing ($p < 0.0286$) was observed for the 1 mm Cu HVL x-ray beam as compared to the 4 mm Cu HVL beam, as measured via clonogenic assays of the vertebral BM myeloid
Figure 6.16: In-vitro data of the clonogenic survival fraction of hematopoietic progenitor (CFU-C) cells exposed to 6 Gy relative to an un-irradiated control group. Using the Mann-Whitney U-test ($p < 0.05$), a statistically significant decrease in survival was observed at the lowest energy beam quality condition when the cells were placed on the BEM in comparison to when no BEM was used, due to dose enhancement of the photoelectrons generated at the interface.

and erythroid progenitors harvested 24 hours post irradiation (Figure 6.17). The differences in cell killing were non-significant when comparing the 4 mm Cu HVL irradiations to the $^{137}$Cs gamma irradiation. Further, the reduced dose rate (0.56 Gy/min, 60 cm SSD) condition consequential to the highly filtered 4 mm Cu HVL beam was not found to lead to a significant difference in cell killing as compared to the 4 mm Cu HVL condition at 35 cm SSD with a higher dose rate (1.45 Gy/min).

6.4 Discussion

The crossing point of the 160 kV (0.62 mm Cu HVL) and the softest 320 kV (1 mm Cu HVL) beam occurred at roughly 45 keV (Figure 6.5), indicating that the 320 kV beam had a higher proportion of low energy photon components below 45 keV despite
Figure 6.17: In-vivo data of the clonogenic survival fraction of myeloid progenitor (CFU-GM) and pre colony forming erythroid progenitor (BFU-E) cells harvested 24-hours post irradiation, from mice exposed to 6 Gy relative to an un-irradiated control group. Using the Mann-Whitney U-test (p < 0.05), a statistically significant decrease in survival was observed at the lowest energy beam quality condition compared to the higher energy radiations of 4 mm Cu HVL at 320 kV and $^{137}$Cs.

The overall higher tube potential. Similarly, another metric of the low energy photon component can be assessed by looking at the area under the curve for photons below 45 keV; this metric was 12% for the 160 kV beam, and 21% for the 320 kV, 1 mm Cu HVL beam. The difference in the proportions of low energy photons between these two beams can be explained by looking at the added filtration amounts needed to achieve these two beam qualities (Table 6.3). The proportion of high energy photons (defined as the area under the curve beyond 120 keV) was 8% for the 160 kV beam and 21% for the 320 kV, 1 mm Cu HVL beam. This substantial difference in high energy components may explain why the 160 kV spectrum had an overall lower beam quality (HVL) compared to the 320 kV 1 mm Cu HVL beam, despite having fewer low energy x-ray components.

The 160 kV beam utilized both a higher Z material, and the overall attenuation
due to the filter was greater than the filtration used for the 320 kV 1 mm Cu HVL beam. For the 160 kV beam, 0.3 mm of added copper \((Z=29)\) was used to achieve the 0.62 mm Cu HVL. For the 320 kV beam, 2 mm of added aluminum \((Z=13)\) was used to achieve the 1 mm Cu HVL. In the most simplistic scenario, radiation attenuation is calculated according to the Beer-Lambert law \(I = I_0e^{-\mu(E)x}\); where \(\mu(E)\) is the linear attenuation coefficient of the filter, and \(x\) is the physical thickness). In the range of 10 keV to 40 keV, the \(\mu(E)\cdot x\) value is more than a factor of four times larger for the copper \((\rho = 8.96 \text{ g/cm}^3)\) used on the 160 kV beam (0.3 mm filter thickness) compared to the aluminum \((\rho = 2.7 \text{ g/cm}^3)\) used on the 320 kV beam (2 mm filter thickness), explaining the more substantial attenuation of low energy x-rays in the 160 kV spectra.

These PDD profiles provide realistic depth dose profiles for small animal irradiation at a range of commonly used photon beam qualities. This work expands on recent published literature that underscores the importance of using realistic mouse-size objects for murine dosimetry, as opposed to larger radiation phantoms such as the solid water-block type that are routinely used for human RT QA; TG-61 recommendations of using solid water phantoms to characterize x-ray irradiator output will overestimate the dose to mice due to differences in scatter generated by the over-sized phantoms (Noblet et al., 2013).

Above a beam quality of 0.5 mm Cu HVL, the backscatter factor has been shown to decrease with increasing beam quality for orthovoltage x-rays in the range of 100-300 kV (Grosswendt, 1990). Increased backscatter may have compensated for the higher attenuation of the primary radiation beam in the 0.62 mm Cu HVL beam, providing one possible explanation of the similarity of the PDD profiles for the 160 kV 0.62 mm Cu HVL and the 320 kV 4 mm Cu HVL beams. The x-ray beam quality as specified in mm Cu HVL is therefore a poor metric of comparison, since HVL does not uniquely characterize an x-ray beam, and this value alone cannot be used to
make inferences about PDD behavior when looking at x-ray beams of different x-ray tube potential. Additionally, from inspection of the PDD data one might expect the 0.62 mm Cu HVL 160 kV beam to have similar dose enhancement to the bone and BM as the 4 mm Cu HVL 320 kV. However the organ dose measurements tell a very different story; the 0.62 mm Cu 160 kV beam produced substantially higher organ dose ratios in the MOBY phantom (relative to the liver) in the bone (3.79) and BM (1.22) as compared to even the softest 320 kV beam studied, which at 1 mm Cu HVL produced ratios of 3.62 and 1.19 for the bone and BM, respectively.

Many factors should be collectively considered when calculating the dose to the murine BM compartment, as evidenced by the micro- and macro-dosimetry findings of both local and systemic dose gradients. Overall, the highest operating tube potential (320 kV vs. 160 kV) and highest filtered (4 mm Cu HVL) beam best emulated the dose distribution of 137Cs gamma irradiation. A large range of differences in the dosimetry for just the small subset of orthovoltage x-ray beams studied here demonstrates the need for standardization of radiation dosimetry practices to provide accurate, reliable, and repeatable radiobiology data across different research institutions.

The geometry used for the Monte Carlo simulation studies did not perfectly replicate the physical irradiation conditions of the in-vitro and in-vivo animal study. The microdosimetry Monte Carlo simulations more closely modeled the in-vivo irradiations, as the complex anatomy of the BM trabeculae were similar among the two. For the in-vitro study, radiation produced on the x-ray system passed first through the cells and then at a normal angle of incidence through the BM material. The in-vitro gamma irradiations using 137Cs required oblique angles of incidence, as a consequence of placing the cell plate on the bottom of the irradiator. This geometry was the only solution for locating the cells in the irradiator, due to the irradiation geometry and the height at which the isotope source was raised to during irradia-
tion. The orientation of the BEM relative to the direction of the incident radiation is important since Compton electrons scatter in a preferred forward direction, and photoelectrons are produced at a slightly preferred forward angle.

The BM architecture and location were both found to affect the dose gradient and average dose to the BM. Most importantly, the trabecular regions in the (i) vertebra and (ii) metaphysis of the femur had a higher proportion of marrow cells residing in close proximity to mineral bone, and therefore resulted in an overall larger fraction of the BM cells receiving increased dose when low energy x-rays were used when compared to trabecular poor regions, such as the femur diaphysis. Trabecular rich anatomical regions such as the vertebrae were chosen for this dose study since the vertebrae contain the majority of the active BM for mice (Boggs, 1984; Colvin et al., 2004).

Good agreement was found among the Monte Carlo computer simulations and both the cell and animal studies of myeloid and erythroid progenitors. While a hematological dose correction factor was not derived from this study, a single prescribed dose of 6 Gy provided cell survival comparisons as needed to demonstrate enhanced dose to the BM for low energy x-rays (1 mm Cu HVL) for both (i) in-vitro overlay on the BEM and (ii) in-vivo whole body irradiation and harvesting of vertebral BM. Concerns over the decreased dose rate by the additional filters added to achieve the 4 mm Cu HVL beam at 320 kV prompted the change of the SSD for this condition to bring the dose rate up from 56 cGy/min (at same SSD as the 1 mm Cu HVL beam condition) to a dose rate of 143 cGy/min as was needed for a fair comparison to the 1 mm Cu HVL condition (145 cGy/min). Both dose rates from these two SSD conditions were studied for the 4 mm Cu HVL beam quality, and no apparent effect was found on the BM colony forming cell survival, as expected from the slow kinetics of the sub-lethal damage repair mechanisms (Steel et al., 1986). Due to the trade-off in dose rate that accompanies a highly filtered x-ray beam (HVL >4 mm
Cu), high kV x-ray generators will outperform low kV x-ray generators when mA, filtration, and all other parameters are equal. When homogeneous dose distributions to the BM are desired, and when a longer irradiation time can be tolerated, a highly filtered x-ray beam and high kV machine should be used.

In this study, the myeloid and erythroid progenitor cell survival was analyzed. These progenitors are a different cell type than the HSC (capable of continuous self-renewal), and more closely represent target cells for acute radiation toxicity (infection, hemorrhaging, and anemia from loss of ascendant blood cell populations).

A most important consideration and key application of the dose findings from this study are in relation to the location and distribution of HSC within the BM. According to stem cell niche studies, HSC commonly reside in close proximity to both blood vessels (in which a high degree of the vascular density occurs at the endosteal surface of the bone) and in contact with osteoblastic cells (Bourke et al., 2009; Ohlstein et al., 2004). HSC may reside in these high dose gradient regions in close proximity to bone, and may thus receive higher doses than the rest of the BM compartment. The dose gradient effects characterized here may be exploited to resolve the relative contribution of the endosteal (next to bone) and vascular (far from bone) stem cell niches.

6.5 Conclusion

This study found that the spatial dose distribution (Equation 6.1, \( D(x) \)) was consistent across different anatomical regions of the mouse at a given radiation energy, but varied according to the different radiation beam qualities. Further, the biological BM distribution (Equation 6.1, \( P(x) \)) varied considerably within the different bone structures of mice, and was shown to have a substantial effect on the average dose to the BM. For anatomical regions of the bone such as the vertebra and femur metaphysis that have a high quantity of trabeculae (BM \(< 40 \mu m \) to mineral bone),
increased overall dose to the BM was observed for low energy x-ray irradiation.

Biological data collected supported the following: (i) low energy x-rays caused increased killing when cells reside in close proximity to high Z materials such as bone, and (ii) low energy x-rays caused increased killing (relative to $^{137}$Cs) to cells in the vertebral BM compartment for the irradiation of live mice. Overall, x-rays of the highest energy and filtration were found to produce dose in the BM more closely approximating $^{137}$Cs gamma irradiation in live mice.
This chapter gives a brief overview of potential directions for future research investigations involving the (i) NanoFOD system and (ii) Monte Carlo analysis of radiation therapy in mice.

7.1 NanoFOD

7.1.1 Alternative Hardware

The NanoFOD systems described and constructed for this dissertation work utilized photo-diode detectors. Next generation NanoFOD systems could be assembled using alternative hardware capable of wavelength discrimination such as charge coupled devices (CCDs). Applications for CCD systems would enable selective wavelength analysis, allowing removal of Cerenkov radiation and other “stem-effect” signals as described by others for plastic scintillating optical fiber use (Archambault et al., 2008). Additionally, cooled radiation detectors may also be investigated for NanoFOD use, to minimize detector noise and improve SNR.
7.1.2 Dosimetry for Imaging Applications

Prior experiments have demonstrated the use of the NanoFOD system to exhibit linear calibration at low x-ray energies down to 80 kV. Imaging procedures such as x-ray CT, fluoroscopy, and planar radiographs utilize x-rays in this energy range, and deliver orders of magnitude lower dose as compared to radiation therapy procedures. Campaigns such as “image gently”\(^1\) and “image wisely”\(^2\) seek to promote radiation safety in pediatric and adult medical imaging. While many arguments can be made about the possible risk or benefit (hormesis) of low radiation doses as encountered in imaging, the wealth of knowledge and improvements in quality control that would result from the tracking, reporting, and monitoring of radiation doses via direct physical measurements can be more easily appreciated. Future work should seek to utilize the NanoFOD for real time dose measurements during imaging procedures for radiographic imaging, interventional fluoroscopy procedures, and x-ray CT.

7.1.3 Dosimetry for External Beam Radiation Therapy

Data previously collected at Duke and UNC showed promise for the use of NanoFOD in high energy applications. The two goals of this preliminary work were to (i) determine if a novel, nano-scintillator based fiber-optic detector would respond linearly with increasing dose on both 6 MV photon and 6 MeV electron beams and (ii) to characterize the dose-rate dependence of the detector for photon and electron beams. The NanoFOD may be a viable candidate for high resolution measurements in external beam treatments, where small field sizes and tight margins are routinely used.

\(^1\) [http://www.imagegently.org/](http://www.imagegently.org/)
\(^2\) [http://www.imagewisely.org/](http://www.imagewisely.org/)
7.1.4 Phosphor Characterization

Additional characterization could be performed to better understand the performance and light yield properties of the scintillation material. Temperature dependence should be studied and reported over the usable range of operation. An example of differences in operation temperature occurred between free in air calibration (25°C) and clinical use in humans (37°C). Plastic scintillator detectors typically exhibit a fraction of a percent change in light output per degree K (0.2%/K, AlO:C (Borroni et al., 2012)).

7.2 Small Animal Organ Dose - Monte Carlo

7.2.1 4D Monte Carlo Studies

Future Monte Carlo dosimetry investigations should consider new geometry to model un-sedated mice during irradiation. When considering the irradiation of live mice, the beam does not necessarily enter the dorsal side of the mouse, and changes in the mouse posture such as standing, sitting, or moving around can impact the dosimetry. In addition, 4D motion due to breathing may be included in the simulation to increase the accuracy and validity of this dosimetry model.

7.2.2 Bone Marrow Dose

Additionally, though it requires further work, the BM doses calculated from the MOBY phantom may in effect provide an estimate of the “Equilibrium Dose” (>100 \( \mu m \) from cortical bone) to the BM. If this is true, future work may seek to use the MOBY phantom to calculate the equilibrium BM doses, and then utilize the microdosimetry results to correct for the trabecular modeling within the BM compartment. This may enable results to be published as a look-up table, so that researchers may be able to correct irradiation times based upon x-ray beam quality to achieve a desired dose to the BM.
7.3 Combining NanoFOD and Monte Carlo

A major goal of Monte Carlo simulation studies is generally to have validated results. Physical measurements are a great way to validate results, since separate and independent data can be collected and directly compared to the model. The NanoFOD system offers a unique tool that may one day be used to validate Monte Carlo measurements to a resolution that has not been achieved by physical detectors in the past.
Appendix A

Code Repository

```python
# -*- coding: utf-8 -*-

@author: matthew belley

This file takes Excel file input from PDF10A detector, provides plot of
data with user input

from __future__ import division, print_function

__author__ = 'Matthew'

import numpy as np
import sys
import os
import glob
from pylab import *
import matplotlib.pyplot as plt
# guiqwt's pyplot: MATLAB-like syntax
from guiqwt.dataset.datatypes import DataSet, BeginGroup, EndGroup
from guiqwt.dataset.dataitems import FloatItem, IntItem, BoolItem,
    ChoiceItem,
    MultipleChoiceItem, ImageChoiceItem,
    FilesOpenItem,
    StringItem, TextItem, ColorItem,
    FileSaveItem,
```

190
from guiqwt.builder import make
from guiqwt.plot import CurveDialog
from guidata.QtGui import QFont

from PyQt4.QtCore import *
from PyQt4.QtGui import *

.app = guidata.qapplication()

def interactive_plot(*items):
    win = CurveDialog(edit=True, toolbar=True, wintitle="Diode Data",
                      options=dict(title='PDF10A Signal', xlabel='Time (s)',
                                    ylabel='Voltage'))
    interactive_plot = win.get_plot()
    for item in items:
        interactive_plot.add_item(item)
    interactive_plot.set_axis_font("left", QFont("Courier"))
    win.get_itemlist_panel().show()
    interactive_plot.set_items_readonly(False)
    win.show()
    win.exec_()

def interactive_plot_raw(*items):
    win = CurveDialog(edit=True, toolbar=True, wintitle="Diode Data",
                      options=dict(title='PDF10A Signal', xlabel='NOT ACCURATE Time (s)',
                                    ylabel='Voltage'))
    interactive_plot = win.get_plot()
    for item in items:
        interactive_plot.add_item(item)
    interactive_plot.set_axis_font("left", QFont("Courier"))
    win.get_itemlist_panel().show()
    interactive_plot.set_items_readonly(False)
    win.show()
    win.exec_()

print("This software imports text file from V4 LabView PDF10A\nAnd Processes Data")
print("[]*10 + \
If you get errors, check to make sure rate and N values are correct for the data--\nset the filename, N, and rate as command line args IN THIS ORDER")
print("Please enter the filename, N, and rate as command line args IN THIS ORDER")
print(sys.argv[1], sys.argv[2], sys.argv[3])

filename = './'+sys.argv[1]
N=float(sys.argv[2]); # number of samples, usually 25
rate = float(sys.argv[3]); # Hz sampling; usually 50

# This means that 25 samples are taken at 50Hz, according to the time-
# stamps provided in the file
# Time stamp is present every 25 values

a = np.loadtxt(fname = filename, delimiter = ',', dtype = np.object, 
skiprows=1)

time,smooth,raw = np.asarray(zip(*a[:])); # This groups by 3's, 
# separates out the columns

# Convert from string to float
raw = raw.astype(float).copy()
smooth = smooth.astype(float).copy()


time_msec = np.asarray(time[:,:N].copy()).astype(float) # pull out 
every 25th value
time_delta = (time_msec-time_msec[0])/1000 
# time stamp of 25th value
avg_time_delta = time_delta[-1] / np.size(time_delta) / N      # in 
seconds, between samples

# Average over N points for each sampling
N_averaged_signal = np.zeros(np.shape(time_delta));
for index in range(len(zeros(np.shape(time_delta))):
    N_averaged_signal[index] = np.mean(raw[N*index:N*(index+1)])

N_averaged_signal_smooth = np.zeros(np.shape(time_delta));
for index in range(len(time_delta)):
    N_averaged_signal_smooth[index] = np.mean(raw[N*index:N*(index 
+1)])

raw = raw.astype(float) # convert to floats

print(type(raw))
print(np.shape(raw))

""" Get better raw time values, using times from time delta """
# Generate raw time stamps, for plotting raw data
raw_time = np.zeros(np.shape(raw))

for index, value in enumerate(time_delta):
    for each in range(int(N)):
        raw_time[index*N+each] = value + (each*1.0/rate)
interactive_plot(make.curve(time_delta, N_averaged_signal)) # time
delta is array
interactive_plot(make.curve(raw_time, raw))

# # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # #
# # Finished
# # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # # #
#
""" coding: utf-8 """
@author: matthew belli

This file takes raw text file input from PM100USB detector, zeros out
the baseline DC signal, and calculates dose integral under the curve

from __future__ import division

"""
Sample data:
PM100USB  SN: P2001128  Firmware: 1.3.0 — Sensor: S150C  SN: 11101802


"""
""" Ensure that no data collection occurs within first 1.5 seconds of on

time

Automatic signal detection threshold can be set (snr to trigger)
Signal is smoothed to improve peak detection (linear smoothing)

"""
import sys
import os
import glob
import numpy as np
import matplotlib.pyplot as plt  # MATLAB-like syntax
import guidata # GUI generation for
dataset editing and display
import guiwt # Efficient 2D data-plotting features
import guiwt.pyplot as plt_ # MATLAB-like syntax
from guidata.dataset.datatypes import DataSet, BeginGroup, EndGroup
from guidata.dataset.datatime import (FloatItem, IntItem, BoolItem,
MultipleChoiceItem, ImageChoiceItem,
FilesOpenItem,
StringItem, TextItem, ColorItem,
FileSaveItem,
FileOpenItem, DirectoryItem,
FloatArrayItem,
DateTimeItem, DateItem)
from guiqwt.builder import make
from guiqwt.plot import CurveDialog
from guidata.Qt.QtGui import QFont
import seaborn as sb
from PyQt4.QtCore import *
from PyQt4.QtGui import *
import scipy.signal as sps

app = guidata.qapplication()
multi_import=True

print('Multi Import Set To: '+repr(multi_import))

# Set formatting for seaborn
sb.set_context("talk")
# override some settings
sb.set_style({'legend.frameon': True})

class Processing(DataSet):
    
    """Importing NP Datasets
    Currently Only One File At a Time is Supported – More Functionality
to be Added
    """

dataDir5 = DirectoryItem("Output Will be Saved To This Directory", default=’.’)
fname = FileOpenItem("Open file, if multi-select \nthis does not matter", ("txt"), default='SqVCir_SANDSX_061112_14.txt')
wiener_true=BoolItem('Yes', 'Wiener Filter Data
(Note: will NOT change average)', default=True);
numberWiener = IntItem('Number of Times to Wiener Filter', default=40)
convNumber = IntItem('Number of Points to Smooth by\nIgnore if Wiener is Set True', default=10)
dontIntegratePlotDose = BoolItem('Yes', 'Do not integrate, plot dose rate\n**If you set this, also define the following 3 items :')
calSlope = FloatItem('Enter Calibration Slope J/R', default=2.054e-12)
fFactor = FloatItem('Enter f-factor', default=0.91)
position = FloatItem('Enter distance per time (microns per second)', default=3.136)

def runPlots(fname):
    convNumber=param.convNumber;
    # GET DATA
    try:
        data=np.loadtxt(fname, dtype=np.float32, comments='#', skiprows =2, usecols=(3,), unpack='True')  # data is Watts
        data=data[:,:-1];  # flip array since time is saved backwards
unsmoothedData=data.copy()
wiener_true=param.wiener_true;
# get time of samples
timeStamp,subSeconds=np.loadtxt(fname, dtype=np.object, comments='#', skiprows=2, usecols=(1,2), unpack='True') # data is WATTS
for index, item in np.ndenumerate(timeStamp):
    timeStamp[index]=item.split(':')[-1]; # only need the last item (seconds)
    subSeconds[index]=subSeconds[index].split('.')[-1]; # only need the last item (1/100 second)

    subSeconds=np.asarray(subSeconds[:1], dtype=np.float32);  # flip array since time is saved backwards
    timeStamp=np.asarray(timeStamp[:1], dtype=np.float32);  # flip array since time is saved backwards

print(' this algorithm currently only tested when sampling time is faster than 1 hz ')
print(timeStamp[1])
print(subSeconds[1])

timeData=[0.0]; deltaSeconds=0.0;  # normalize
for index in range(len(timeStamp)-1):  # STOP at n-1 elements in time stamp data
    # check largest division first, handle roll over after 60
    if (timeStamp[index+1] < timeStamp[index]):  # this is a roll over
        deltaSeconds+=60.0+timeStamp[index+1]-timeStamp[index]
    else:
        deltaSeconds+=timeStamp[index+1]-timeStamp[index]
    # Now handle 1/100 seconds below; goes from 0 to 99
    if subSeconds[index+1] < subSeconds[index]:
        deltaSeconds+=(subSeconds[index+1] - subSeconds[index]) /100.0
    else:
        deltaSeconds+=(subSeconds[index+1] - subSeconds[index]) /100.0
    timeData.append(deltaSeconds)
print(' Average Delta T (seconds): ' + repr((timeData[-1]-timeData[1])/len(timeData)))

plt.figure(figsize=(5.5,4))
plt.title('TIME DATA, deltaT')
plotTime=[]
for xx in range(len(timeData)-1):
    plotTime.append(timeData[xx+1]-timeData[xx])
plt.plot(plotTime, 'o')

# smoothing
kernel=np.ones(convNumber)/convNumber
if wiener_true is False:
data = np.convolve(data, kernel, mode='same')

else:
    for yy in range(param.numberWiener):
        data = sps.wiener(data);

def plot(*items):
    win = CurveDialog(edit=True, toolbar=True, wintitle="Dose Data",
                      options=dict(title='Raw Data', xlabel='Time (s)',
                                    ylabel='Power (W)'))
    plot = win.get_plot()
    for item in items:
        plot.add_item(item)
        plot.set_axis_font("left", QFont("Courier"))
    win.set_items_readonly(False)
    win.show()
    win.exec_()

if param.dontIntegratePlotDose == False:
    # Data written in text file is in reverse time order
    slopeData = np.zeros((len(data)-1));
    for slopeIterate in range(len(data)-1):
        slopeData[slopeIterate]=data[slopeIterate+1]-data[slopeIterate]
    minSlopeIndex = np.argmin(slopeData);  # Returns the index
    maxSlopeIndex = np.argmax(slopeData);
    minSlope = np.min(slopeData);
    maxSlope = np.max(slopeData);

    print('Min and Max slope: ' + repr(minSlope) + ', ' + repr(maxSlope))

for iterate in range(len(data)):
    # Look from min slope to the right for zero for end time
    if slopeData[minSlopeIndex+iterate] >= 0:
        endTime = timeData[minSlopeIndex+iterate];
        endIndex = minSlopeIndex+iterate
        print('End Time: ' + repr(endTime))
        break

for iterate in range(len(data)):
    # Look from max slope to the left for zero for end time
    if slopeData[maxSlopeIndex-iterate] <= 0:
        startTime = timeData[maxSlopeIndex-iterate];
        startIndex = maxSlopeIndex-iterate
        print('Start Time: ' + repr(startTime))
        break

    # Need to pass the values on startTime, endTime,
try:
    averageSignal=np.average(unsmoothedData[startIndex:endIndex])  # in Watts
    bkgData=np.concatenate((unsmoothedData[:startIndex-1],
                            unsmoothedData[endIndex+1:])).copy()  # In Watts
    bkgAvg=np.average(bkgData)  # Watts, Average all background data (signal has been removed)
    netSignal=averageSignal-bkgAvg  # Watts
    integralNetSignal=(endTime-startTime)*netSignal  # Joules, multiply avg by on time
    print('Net Integrated Signal (J): %.4g % integralNetSignal')
    print('net integrated signal is not smoothed data, it is original data')

""" Uncertainty analysis """
try:
    bkgSTDEV=np.std(bkgData)*(endTime-startTime)/np.sqrt(len(bkgData))
    signalSTDEV=np.std(unsmoothedData[startIndex:endIndex])*(endTime-startTime)/np.sqrt(len(unsmoothedData[startIndex:endIndex]))
    print('STDERR due to background (Percent): %.3g' % (bkgSTDEV))
    print('STDERR of NET integral signal (Percent): %.3g' % (signalSTDEV))
"""

Display data to user
Flip data in time

except Exception, err:
    pass

e except Exception, err:
    pass

try:
    # first figure just to visualize background signal
    plt.figure(figsize=(5.5,4))
    plt.title('Background Data', fontsize='10')
    plt.xlabel('Data Point', fontsize='12')
    plt.ylabel('Power (W)', fontsize='12')
    plt.plot(bkgData, '-or')
    plt.axhline(y=bkgAvg, xmin=0, xmax=len(bkgData), label='Avg Bkg', color='g', linestyle='--')  #
    plt.legend(loc=1)

    # new figure for data
    plt==plt.figure(figsize=(5.5,4))
```python
plt.plot(timeData, unsmoothedData, 'o', label='Raw', markersize=4)
plt.axhline(y=bkgAvg, xmin=0, xmax=len(bkgData), label='Avg Bkg', color='g', linestyle='--')
plt.plot(timeData, data, '-b', label='Smoothed')

# set axis to fit scaling for legend, etc.
xmax = np.max(timeData) * 1.05;
ymin = np.min(unsmoothedData) - 0.1 * np.abs(np.min(unsmoothedData));
ymax = np.max(unsmoothedData) + 0.3 * np.abs(np.max(unsmoothedData));
plt.axis([0, xmax, ymin, ymax])

# Fill between dose data and zero data
plt.fill_between(timeData[startIndex:endIndex + 1], data[startIndex:endIndex + 1], bkgAvg, facecolor='y', alpha=0.5, label='Integral')

# print relevant values
plt.text(0.5 * xmax, 0.95 * ymax, '{: >25}'.format('Integral Net ($J$):') + '{: <10}'.format('%.4g % integralNetSignal),
fontsize='9', horizontalalignment='right'
)
plt.text(0.5 * xmax, 0.89 * ymax, '{: >25}'.format('STDErr Net ($J$):') + '{: <10}'.format('%.4g % (signalSTDEV)),
fontsize='9', horizontalalignment='right'
)

plt.legend(loc=1, fontsize='10')
plt.xlabel('Time (s)', fontsize=12, fontweight='bold')
plt.ylabel('Power (W)', fontsize=12, fontweight='bold')
titleName=fname.split('\\')[1]
print(titleName)
plt.title(titleName[-1], fontsize='10')    # Title name is only name of the file

try:
p1.savefig(fname+'.png', bbox_inches='tight', dpi=800)  # Save to directory with raw data
del p1;
except:
    print("Failed to save figure: "+repr(titleName[-1]))
except Exception, err:
    print("Failed for File: ' +fname)
    print(repr(err))
```

198
pass

elif param.dontIntegratePlotDose == True:
    try:
        print('Only Displaying Dose Rate Plot')
        plt.figure(figsize=(5.5,4))
        plt.plot(timeData*param.position, data/param.calSlope*param.fFactor, '-b', label='Smoothed Data')
        plt.plot(timeData*param.position, unsmoothedData/param.calSlope*param.fFactor, 'or', label='Original Data')
        plt.legend(loc=2)
        plt.xlabel('Position (microns)', fontsize=12, fontweight='bold')
        plt.ylabel('Dose Rate (cGy/s)', fontsize=12, fontweight='bold')
    except Exception, err:
        print('Failed save for File: '+fname)
pass

print('This script uses the built in time stamps in the output file')

if multi_import==True:
    print('Multi import selected')
    var = raw_input("Enter multi-import directory: ")
    path = var
    print(path)
    param = Processing()
    param.edit()
    print('Inputs:')
    print param
    print('>>>>>>')
    for infile in glob.glob(os.path.join(path, '*.*')):
        fname=infile
        print "current file is: " + infile
        runPlots(fname)
        plt.show()
else:
    param = Processing()
    param.edit()
    print('Inputs:')
    print param
    print('>>>>>>')
    fname=param.fname
    runPlots(fname)
    plt.show()
Appendix B

Standard Operating Procedures

B.1 Pre-Measurement NanoFOD Integrity Check

The following is a standard operating procedure (SOP) written to test and verify functionality of the NanoFOD system prior to performing clinical measurements.

These steps will verify proper equipment operation and should be carried out immediately before performing a NanoFOD measurement. This check should take no more than 5-10 minutes to complete.

1. Verify laptop battery is charged. If battery is low, plug in AC adapter.
2. Verify USB from DAQ is connected to laptop and that hardware is detected.
3. Check integrity of the Cerenkov filter in diode, by loosening the black cap on the diode. Verify type of filter (550 vs. 590 nm). Gently, tighten the black cap back in place being
careful not to damage the glass filter.

4. Inspect all electrical connections and grounding lines are tight and secure. There are three ground connections: diode to chassis, diode to SMA, and chassis to DAQ.

5. Run a background data set with diode powered on. Remove red cap during the data collections. The diode signal should be roughly 0.15-0.16 V for background (cap on) and ≈11 V or more when saturated with room light (red cap off).

6. Inspect integrity of the NanoFOD fiber. Shine laser light through the fiber via the SMA-905 connector. Look for the laser light at the other end of the fiber. This confirms the fiber is in-tact.

7. If a surge protector is to be used, ensure that the ‘‘reset’’ button is in the ‘‘on’’ position. Power is properly supplied to the diode if the green LED indicator light is illuminated on the AC/DC diode power supply.

Starting data collection (steps take <5 min):

1. Verify fiber SMA is connected to diode -- do not over tighten, as this will damage the Cerenkov filter.

2. Place diode in lead shield, if necessary. Avoid bending the fiber in tight radii if possible.

3. Open the V6 LabView software. Set 50 Hz sampling rate, N=25 samples.
4. Click ‘run’. Name the file, using ‘.xlsx’ as the extension.

5. Verify that once data collection is started, you see the LabView plots updating in real time. The background signal MUST be \( \approx 0.15-0.2 \) V depending on the ambient conditions. If the signal is higher than this, the fiber is not working correctly.

These steps are meant to be carried out the night before a NanoFOD measurement (steps take <5 min).

1. Charge laptop.

2. Supply power to diode, with diode switched to ‘ON’ for warm-up.

3. Make sure a fiber is sanitized and ready for use. A backup fiber should be available.

B.2 Fiber Acceptance Testing

The purpose of this SOP was to verify that the quality of fibers that were newly fabricated met a minimum standard of quality and performance.

1. For the visible inspection, the scintillation particle should be clearly visible on tip of fiber under short wave UV excitation.

2. For sensitivity testing, all new fibers should be tested on an x-ray cabinet to verify that the fiber assembly is properly collecting light and to document the light quantity. Depending on the application, if the fiber light does not meet a certain minimum threshold, the fiber will be considered to fail the acceptance test, and a new phosphor will be added to the tip.
3. Test conditions using Faxitron x-ray cabinet irradiator system: 130kV, 5mA. Tape fiber to top of shelf #7. Use Thor equipment PM100USB/S150C.

4. For mechanical and durability testing, the fiber fiber should be inspected to be free from scratches.
Appendix C

Additional Equations

C.1 Radiation Quantities

Effective dose is a radiation concept that may be used to estimate risk based on the weighted summation of the dose to individual organs, defined as:

\[ E = \Sigma_T(w_T \times H_T) \]  \hspace{1cm} (C.1)

Where \( H_T \) is the equivalent dose to a given tissue and \( w_T \) is the ICRP tissue weighting factor (ICRP, 2007).

C.2 Optical Fiber

Optical fibers (> 8 \( \mu m \) core diameter) may collect light that propagates along the meridian of the fiber (known as meridional rays) if the light rays are incident within a critical angle \( (\theta_a) \). In 3D, this critical angle forms a cone, and the size of the cone is specified by a value known as the numerical aperture (NA). The NA of a fiber is
defined as (Senior, 1992):

\[ NA = n_0 \cdot \sin(\theta_a) \]  \hspace{1cm} (C.2)

\[ NA = (n_1^2 - n_2^2)^{1/2} \]  \hspace{1cm} (C.3)

Where \( n_0 \) is the refractive index of the medium at the tip of the fiber and \( \theta_a \) is the angle of acceptance for meridional ray propagation. Relating NA to the fiber properties, \( n_1 \) and \( n_2 \) are the refractive indices of the core and cladding respectively.

Additionally, the photons should be within the transmission wavelength range of the optical fiber (UV/VIS or VIS/IR) to be transmitted to the diode. For the NanoFOD studies, both low OH ("dry") and high OH ("wet") fibers were used, since the 611 nm transmission wavelength was similarly transmissive in both.

C.3 Clinical Ion Chamber Measurements

The PTW TN30006 (Freiburg, Germany) farmer type ionization chamber was operated at +300 V. This chamber was calibrated at an ADCL in water at 5 cm depth using \(^{60}\)Co. The calibration data sheet reported the value of \( N_{D,w} = 5.305 \times 10^7 \text{ Gy}/\text{C} \) with an uncertainty of 1.3%.

To correct for the pressure and temperature, the following equation was used from TG-51 (Almond et al., 1999):

\[ P_{TP} = \frac{273.2 + T}{273.2 + 22.0} \times \frac{101.33}{P} \]  \hspace{1cm} (C.4)

Where \( T \) is the temperature (Celsius) in the water or air of the environment surrounding the chamber, and \( P \) is the pressure in units of kPa.
C.4 Dosimetry Equations

Tissue maximum ratio (TMR) is calculated according to (Holt et al., 1970):

\[
TMR(d, W_d) = \frac{D(d, W_d, SSD + d)}{D(t, W_d, SSD + d)} \tag{C.5}
\]

Where \(d\) is the depth, \(SSD\) is the source-to-surface distance, \(W_d\) is the field size at depth \(d\), \([D(d, w_d, SSD + d)]\) is the dose at depth \(d\) in tissue, and \([D(t, w_d, SSD + d)]\) is the dose at maximum buildup depth \(t\).

The roentgen to dose conversion factor (f-factor) for the dose to water was calculated according to (Ma et al., 2001):

\[
f_{\text{water}}(E) = 0.876 \left[ \frac{cGy}{R} \right] \times \frac{\mu_{\text{en}}(E)_{\text{water}}}{\mu_{\text{en}}(E)_{\text{air}}} \tag{C.6}
\]

Where 0.876 [cGy/R] is the exposure-to-dose in dry air conversion factor and \(\frac{\mu_{\text{en}}}{\rho}(E)\) is the mass-energy absorption coefficient for a given material.
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Zhong, N., Morris, G. M., Bacarian, T., Rosen, E. M., and Avraham Dilmanian,
Biography

Name: Matthew D Belley
Date of Birth: February 18, 1989
Place of Birth: Massachusetts, USA

Education

Duke University: Durham, NC
Ph.D. Medical Physics (September 2015)

Rensselaer Polytechnic Institute: Troy, NY
BS: Mechanical and Nuclear Engineering (May 2011, Summa Cum Laude)

Honors, Awards, and Fellowships

1. Excellence in PhD research award (Spring 2014)
2. First Place at the NC HPS Student Research Competition (Spring 2013)
3. US NRC Health Physics Fellowship HQ-12-G-38-0022 (2012-Present)
4. NIH Cross-Disciplinary Training Grant T32-EB007185 (2011-2012)
5. 3x Student travel award for 2012, 2013, 2015 Annual HPS Meeting
6. 2x Scholar in Training (SIT) travel award for 2013 and 2014 Radiation Research Society Meeting


8. Recipient of RPI Founder’s Award of Excellence (2009)


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