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Optical dosimetry tools and Monte Carlo based methods for applications in image guided optical therapy in the brain

Akshay N Prabhu Verleker
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By Akshay N Prabhu Verleker

Entitled
OPTICAL DOSIMETRY TOOLS AND MONTE CARLO BASED METHODS FOR APPLICATIONS IN IMAGE GUIDED OPTICAL THERAPY IN THE BRAIN

For the degree of Doctor of Philosophy

Is approved by the final examining committee:

Dr. Keith Stantz
Chair

Dr. Shuang Liu

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Dr. James Schweitzer

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Approved by Major Professor(s): Dr. Keith Stantz

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Head of the Departmental Graduate Program

Date: 6/21/2016
OPTICAL DOSIMETRY TOOLS AND MONTE CARLO BASED METHODS FOR APPLICATIONS
IN IMAGE GUIDED OPTICAL THERAPY IN THE BRAIN

A Dissertation
Submitted to the Faculty
of
Purdue University
by
Akshay N Prabhu Verleker

In Partial Fulfillment of the
Requirements for the Degree
of
Doctor of Philosophy

August 2016
Purdue University
West Lafayette, Indiana
Dedicated to my grandfather whose “Science Bug” bit me early in life.
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It would not have been possible to come this far without the love and support (emotional and technical) from my parents Dr. Narayan and Dr. Shitala Prabhu Verleker, my wife and better-half Shweta, my sister Sayali and brother Ashwin.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xviii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>xix</td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Overview</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Application in Optically Stimulated Drug Release</td>
<td>2</td>
</tr>
<tr>
<td>1.3 Applications Requiring Quantification of NIR Light Delivery</td>
<td>5</td>
</tr>
<tr>
<td>1.4 Light Transport Theory</td>
<td>7</td>
</tr>
<tr>
<td>1.5 A GPU based 3D Monte Carlo for photon transport</td>
<td>10</td>
</tr>
<tr>
<td>1.6 An Empirical Photon Propagation Algorithm</td>
<td>12</td>
</tr>
<tr>
<td>1.7 A Titanium Dioxide based Optical Dosimetry Probe</td>
<td>13</td>
</tr>
<tr>
<td>2 SPECIFIC AIMS</td>
<td>15</td>
</tr>
<tr>
<td>2.1 Specific Aim1: Develop, build and test an optical dosimetry probe</td>
<td>16</td>
</tr>
<tr>
<td>and advance 3D Monte Carlo photon transport code capable of measuring and simulating the local photon fluence and dose in optical tissue phantoms</td>
<td>16</td>
</tr>
<tr>
<td>2.2 Specific Aim2: Simulate and validate the absolute photon fluence in homogenous and heterogeneous brain tissue phantoms resembling white matter, gray matter, skull bone and tumor</td>
<td>17</td>
</tr>
<tr>
<td>2.3 Specific Aim3: Devise an empirical model and algorithms capable of simulating for photon propagation in complex heterogeneous tissues in real-time</td>
<td>17</td>
</tr>
</tbody>
</table>
Specific Aim 4: Investigate the feasibility of using the above tools and methods to optimize optical therapeutic protocols in human skull bones using image-guided techniques...

3 SPECIFIC AIM 1: OPTICAL SIMULATION AND DOSIMETRY TOOLS

3.1 Introduction

3.1.1 Monte Carlo Algorithm

3.1.2 Optical Dosimetry Probe

3.2 Materials and Methods

3.2.1 Monte Carlo Beam Optimization

3.2.2 Optical Dosimetry Probe Design and Calibration

3.3 Results

3.3.1 Monte Carlo Optimization

3.3.2 Optical Probe Calibration

3.4 Discussion

4 SPECIFIC AIM 2: VALIDATION OF MONTE CARLO IN TISSUE PHANTOMS

4.1 Introduction

4.1.1 Optical Phantom Characteristics

4.1.2 Spectro-photometer Calibration

4.1.3 Probe and Monte Carlo based validation of intralipid

4.2 Materials and Methods

4.2.1 Characterization of Optical Phantoms

4.2.2 Validation of 3D Monte Carlo in brain phantoms using Optical dosimetry

4.3 Results

4.3.1 Optical Dosimetry and Monte Carlo Validation in Homogeneous Phantoms

4.3.2 Optical Dosimetry and Monte Carlo Validation in Heterogeneous Brain Phantoms

4.4 Discussion
<table>
<thead>
<tr>
<th>APPENDICES</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix A</td>
<td>Validating Scattering Coefficient of Intralipid through Probe Measurements</td>
</tr>
<tr>
<td>Appendix B</td>
<td>Optical Dosimetry in a Goat Skull Phantom</td>
</tr>
<tr>
<td>VITA</td>
<td>151</td>
</tr>
</tbody>
</table>
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 4.1 Optical Properties of Brain Tissues [79, 80]</td>
<td>52</td>
</tr>
<tr>
<td>Table 4.2 Phantom Composition [63]</td>
<td>53</td>
</tr>
<tr>
<td>Table 4.3 % Mismatch Error in Homogeneous Phantom along beam axis (z)</td>
<td>60</td>
</tr>
<tr>
<td>Table 4.4 % Mismatch Error in Homogeneous Phantom perpendicular to beam axis (z)</td>
<td>61</td>
</tr>
<tr>
<td>Table 4.5 % Mismatch Error in Heterogeneous Phantom along beam axis (z)</td>
<td>63</td>
</tr>
<tr>
<td>Table 4.6 % Mismatch Error in Heterogeneous Phantom perpendicular to beam axis (z)</td>
<td>63</td>
</tr>
<tr>
<td>Table 5.1 Weights derived for Brain Tissue Phantoms [63]</td>
<td>76</td>
</tr>
<tr>
<td>Table 5.2 Weights derived for Brain Tissues</td>
<td>77</td>
</tr>
<tr>
<td>Table 5.3 Weights derived to obtain fluence buildup</td>
<td>96</td>
</tr>
<tr>
<td>Table 6.1 Optical properties of skull bone measured at 800nm wavelength in different studies [80, 100-102]. The anisotropy factor (g) is 0.9.</td>
<td>99</td>
</tr>
<tr>
<td>Table 7.1 Optical dosimetry probe composition (diameter&lt;2mm) and % isotropicity variation [68, 69]</td>
<td>120</td>
</tr>
<tr>
<td>Table 7.2 Methods for photon propagation [61, 107-111]. Estimated simulation times for a head study.</td>
<td>123</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Figure 1.1 (a) Light-induced release of DAPI (4',6-diamidino-2-phenylindole) within H1299 lung cancer cells. (b) Left: H1299 lung cancer cells containing DAPI prior to illumination and on the right: after NIR exposure. (Input fluence: 1 W/cm², NIR wavelength: 800 nm, 5 minute exposure duration). No major cytotoxicity was observed in assay studies post illumination. (c) Macrophages incubated with gold-silica-nanoshells-red fluorescent microspheres complexes [8, 9]. Intra-cellular accumulation of these fluorescent molecules is seen in the transmission electron micrograph within the cytoplasm vacuoles (see arrow 2). (c) Images using fluorescence microscopy indicate microsphere accumulation through red fluorescence (580/605 nm) [8, 9].</td>
<td>4</td>
</tr>
<tr>
<td>Figure 3.1 Flowchart of the Monte Carlo algorithm for photon propagation [61]</td>
<td>20</td>
</tr>
<tr>
<td>Figure 3.2 Optical dosimetry probe [68]</td>
<td>23</td>
</tr>
<tr>
<td>Figure 4.1 Measurement of light transmission in a Spectro-photometer. A fine pencil beam of a specific wavelength is transmitted across a sample contained in a glass cuvette with a fixed path length. The absorbance of the sample is calculated using Beer Lambert’s law [78].</td>
<td>46</td>
</tr>
</tbody>
</table>
Figure 4.2 Calibration curve of spectrophotometer measured absorbance versus %Concentration of India ink. The error bars represent minimum and maximum absorbance.

Figure 4.3 Intralipid Scattering: Upper figure represent measured values of scattering coefficients ($\mu_s$ and $\mu_s1$) versus %Concentration of Intralipid using a spectrophotometer. The error bars represent minimum and maximum values. Lower figure shows extrapolated values from the linear relationship derived from the measured values.

Figure 4.4 Setup for Optical dosimetry in a liquid phantom. The optical dosimetry probe is translated within a plexiglas cuvette filled with liquid phantom, and illuminated by an NIR source.

Figure 4.5 Optical dosimetry in white and gray matter phantoms. The photon source used is an integrating sphere connected to a pulsating laser source. The graphs show the exponential decrease of photon fluence along the beam axis in white and gray matter mimicking phantoms. The Monte Carlo generated fluence closely matches the fluence measured by the probe.

Figure 4.6 Optical dosimetry in white matter, gray matter and skull bone phantoms. The photon source used is an optical fiberguide (connected to a pulsating laser source) with a super-Gaussian beam distribution. The Monte Carlo generated fluence closely matches the fluence measured by the probe. This shows that the Monte Carlo beam modeling can be reliably used as a reliable estimator of photon energy distribution in tissue phantoms.
Figure 4.7 Lateral beam profile measurement using optical dosimetry probe and validation by Monte Carlo in homogeneous phantoms. (A) Beam profile in air using calorimeter. Optical dosimetry measurements validated MC simulated lateral beam profiles in phantoms of: (B) white matter, (C) gray matter and (D) skull bone, i.e., perpendicular to the beam axis. The measurements were normalized along the illumination axis. Cuvette dimensions: 5.3cm x 4.6cm x 3.1cm, thickness = 0.4cm.  

Figure 4.7 Continued

Figure 4.8 Validation of Monte Carlo in a heterogeneous phantom (1.1cm skull agar, 1.1cm gray matter agar and 5.9cm white matter liquid). Lateral profile measurements (in the white matter phantom solution) are shown on the left while axial comparison is on the right. The depth shown by z is the distance from the gray matter agar surface. Cuvette dimensions: 9.4cm x 9.4cm x 10.9cm, thickness = 0.3cm.

Figure 5.1 The Empirical photon propagation [64]: The photons in a voxel is propagated to neighboring voxels using scatter weights.

Figure 5.2 Integral or accumulation of fluence in a voxel. [64]. The directional fluences such as forward (If), diagonal upwards (Id), diagonal downwards (Idb) and side (Is), entering a voxel are weighted and summed using forward (wt1) and diagonal weights (wt2). Fluence is redistribution conserved by ensuring that (wt1 + 4 x wt2) = 1.
Figure 5.3 A) Implementation of the 3D Empirical algorithm using nested loops. Photons are propagated in the simulation by iterating over a 3D matrix. The matrix dimensions in the x, y, z coordinates are dim1, dim2 and dim3 respectively, while (i, j, k) are (x, y, z) coordinates of a voxel in the volume. B) Iterative routine to run the Empirical algorithm. In each iteration we check if the sum of the residual fluences are below a certain threshold. If the residual fluences are still high, we run the empirical code iteratively to ensure that the residual fluences have exited the volume. In our study we use 14 iterations for the neonatal head simulations, while 1 iteration is sufficient for homogeneous phantoms. The iterative routine is seen to be more effective for highly scattering tissues with a significant amount of back-scatter.

Figure 5.3 Continued

Figure 5.4 Optimization phase for Brain Tissue Phantoms. The optical properties of phantom materials (India ink and Intralipid) from table 4.2, are used by the MC. A flat broad beam (2cm diameter) is simulated using Monte Carlo and the Empirical algorithm is optimized to match the Monte Carlo with the identical illumination conditions [63].

Figure 5.5 Optimization phase for Brain Tissues. The brain tissue properties from table 4.1 are used by the Monte Carlo. A flat broad beam (2cm diameter) is simulated using Monte Carlo and the Empirical algorithm is optimized to match the Monte Carlo with the identical illumination conditions.

Figure 5.6 Lateral Beam profile comparison between Empirical and Monte Carlo for Gray Matter tissue. A flat broad beam (2cm diameter) is simulated.
<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 5.7 Lateral Beam profile comparison between Empirical and Monte Carlo for White Matter tissue. A flat broad beam (2cm diameter) is simulated.</td>
<td>80</td>
</tr>
<tr>
<td>Figure 5.8 Lateral Beam profile comparison between Empirical and Monte Carlo for Skull Bone tissue. A flat broad beam (2cm diameter) is simulated.</td>
<td>81</td>
</tr>
<tr>
<td>Figure 5.9 Lateral Beam profile comparison between Empirical and Monte Carlo for Astrocytoma Tumor tissue. A flat broad beam (2cm diameter) is simulated.</td>
<td>82</td>
</tr>
<tr>
<td>Figure 5.10 Comparison of the Empirical algorithm with Monte Carlo and Probe measured fluence in brain phantoms resembling white matter, gray matter and skull bone. The illumination source used is a super-Gaussian beam, which is emulated by the Monte Carlo and the Empirical algorithm. The empirical approach is a close approximation of the Monte Carlo and the probe over the range of optical properties of brain tissues.</td>
<td>84</td>
</tr>
<tr>
<td>Figure 5.11 Simulation of a head phantom for comparing the Empirical and Monte Carlo models in heterogeneous brain tissues.</td>
<td>86</td>
</tr>
<tr>
<td>Figure 5.12 Comparison of photon energy distribution between the Empirical algorithm and Monte Carlo in a head phantom, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.11).</td>
<td>87</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Figure 5.13</td>
<td>Comparison of photon fluence distribution between the Empirical algorithm and Monte Carlo in a head phantom, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.11).</td>
</tr>
<tr>
<td>Figure 5.14</td>
<td>Comparison of photon energy distribution images (2D) between the Empirical algorithm and Monte Carlo in a normal head phantom.</td>
</tr>
<tr>
<td>Figure 5.15</td>
<td>Simulation of a head phantom with tumor (astrocytoma) for comparing the Empirical and Monte Carlo models in heterogeneous brain tissues.</td>
</tr>
<tr>
<td>Figure 5.16</td>
<td>Comparison of photon energy distribution between the Empirical algorithm and Monte Carlo in a head phantom with tumor, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.15).</td>
</tr>
<tr>
<td>Figure 5.17</td>
<td>Comparison of photon fluence distribution between the Empirical algorithm and Monte Carlo in a head phantom with tumor, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.15).</td>
</tr>
<tr>
<td>Figure 5.18</td>
<td>Comparison of photon energy distribution images (2D) between the Empirical algorithm and Monte Carlo in a head phantom with tumor (astrocytoma).</td>
</tr>
<tr>
<td>Figure 5.19</td>
<td>Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for White Matter.</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Figure 5.20 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for Gray Matter</td>
<td>94</td>
</tr>
<tr>
<td>Figure 5.21 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for Skull Bone</td>
<td>95</td>
</tr>
<tr>
<td>Figure 5.22 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for Tumor (Astrocytoma)</td>
<td>95</td>
</tr>
<tr>
<td>Figure 6.1 Setup to measure the optical transmission of NIR light through the skull bone. The source used is an optical fiberguide connected to a laser. The NIR fluence collected by the probe tip is carried by an optical fiber to a PIN photodiode circuit, whose electrical output is read using an oscilloscope (right)</td>
<td>101</td>
</tr>
<tr>
<td>Figure 6.2 Skull bone sample (top portion) used in the experiment. The dosimetry probe is also seen</td>
<td>102</td>
</tr>
<tr>
<td>Figure 6.3 Optical dosimetry setup for lateral beam profile measurement in skull sample.</td>
<td>102</td>
</tr>
<tr>
<td>Figure 6.4 Optical dosimetry setup for lateral beam profile measurement in a skull sample. This shows the illumination setup using the optical fiberguide source</td>
<td>103</td>
</tr>
<tr>
<td>Figure 6.5 The CT image of a skull bone is processed in Matlab to extract the source directional vector (A) and in-plane source vector (B) by drawing lines (blue) on the image and extracting the end points of the lines to calculate the vectors. The third vector is the cross product of these two vectors and is in the plane of the source</td>
<td>105</td>
</tr>
<tr>
<td>Figure</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Figure 6.6 Percentage fluence transmitted for phantoms 1-4 measured using the probe calorimeter setup.</td>
<td>107</td>
</tr>
<tr>
<td>Figure 6.7 Percentage fluence transmitted for phantoms 6-9 measured using the probe calorimeter setup.</td>
<td>108</td>
</tr>
<tr>
<td>Figure 6.8 Percentage fluence transmitted for phantoms 10-11 measured using the probe calorimeter setup.</td>
<td>109</td>
</tr>
<tr>
<td>Figure 6.9 Skull thicknesses measured across skull samples using CT image data. Measurement points: Phantom1 (1-5), Phantom2 (6-10), Phantom3 (11-15), Phantom4 (16-20), Phantom5 (21-25), Phantom6 (26-30), Phantom7 (31-35), Phantom8 (36-40), Phantom9 (41-45), Phantom10 (45-50).</td>
<td>109</td>
</tr>
<tr>
<td>Figure 6.10 Lateral beam profile (fraction transmitted) measured using the dosimetry probe in air and water 0.5mm from the inner skull surface.</td>
<td>110</td>
</tr>
<tr>
<td>Figure 6.11 MC simulated fluence profiles along beam axis for a homogeneous skull medium generated using Monte Carlo simulations for three sets optical properties of the skull bone (Ugrynova et al, Pifferi et al, Firbank et al, and Bashkatov et al). A broad beam super-Gaussian NIR source (800nm wavelength) was simulated.</td>
<td>111</td>
</tr>
<tr>
<td>Figure 6.12 MC simulated lateral fluence profiles at different depths (z=0,2,4,6mm) for a homogeneous skull medium generated using Monte Carlo simulations for three sets optical properties of the skull bone (Ugrynova et al, Pifferi et al, Firbank et al, and Bashkatov et al). A broad beam super-Gaussian NIR source (800nm wavelength) was simulated.</td>
<td>112</td>
</tr>
</tbody>
</table>
Figure 6.13 Comparison of % transmitted fluence between the calorimeter-probe measurements and the Monte Carlo. The error bars in the probe measurements represent the maximum and minimum intensities in the 3 averages, while the error bars in the Monte Carlo are the minimum and maximum fluences between the 3 optical models (see table 6.1). ................................................................. 113

Figure 6.14 Comparison of lateral profiles measured using dosimetry probe with the Monte Carlo in water. ......................................................................................................................... 114

Figure 6.15 Boundary conditions simulated using the CT image-guided Monte Carlo. 115

Figure 8.1 MC simulation of temporal pulse width versus depth in a heterogeneous head phantom (see figure 5.11) for an input pulse 1ns wide. The pulse width was measured by calculating the Full Width at Tenth Maximum (FWTM) to analyze the temporal beam spread. .................................................................................. 129
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIR</td>
<td>Near Infra-red</td>
</tr>
<tr>
<td>MCX</td>
<td>Monte Carlo Extreme (GPU based Monte Carlo by Fang group)</td>
</tr>
<tr>
<td>MC</td>
<td>Monte Carlo</td>
</tr>
<tr>
<td>GPU</td>
<td>Graphical Processor Unit</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full Width at Half Maximum</td>
</tr>
<tr>
<td>FWTM</td>
<td>Full Width at Tenth Maximum</td>
</tr>
<tr>
<td>OPO</td>
<td>Optical Parametric Oscillator</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>TiO₂</td>
<td>Titanium Dioxide</td>
</tr>
<tr>
<td>RMS</td>
<td>Root Mean Square</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>OPO</td>
<td>Optical Parametric Oscillator</td>
</tr>
</tbody>
</table>
ABSTRACT

Prabhu Verleker, Akshay N. Ph.D., Purdue University, August 2016. A Therapeutic Protocol for Treatment of Brain Metastasis through Optically Stimulated Drug Release. Major Professor: Keith Stantz.

Purpose: The long-term goal of this research is to determine the feasibility of using near infra-red light to stimulate drug release in metastatic lesions within the brain. In this work, we focused on developing the tools needed to quantify and verify photon fluence distribution in biological tissue. To accomplish this task, an optical dosimetry probe and Monte Carlo based simulation code were fabricated, calibrated and developed to predict light transport in heterogeneous tissue phantoms of the skull and brain. Empirical model (EM) of photon transport using CT images as input were devised to provide real-time calculations capable of being translated to preclinical and clinical applications.

Methods and Materials: A GPU based 3D Monte Carlo code was customized to simulate the photon transport within head phantoms consisting of skull bone, white and gray matter with differing laser beam properties, including flat, Gaussian, and super-Gaussian profiles that are converging, parallel, or diverging. From these simulations, the local photon fluence and tissue dosimetric distribution was simulated and validated.
through the implementation of a novel titanium-based optical dosimetry probe with an isotropic acceptance and 1.5mm diameter. Empirical models (EM) of photon transport were devised and calibrated to MC simulated data to provide 3D fluence and optical dosimetric maps in real-time developed around on a voxel-based convolution technique. Optical transmission studies were performed using human skull bone samples to determine the optical transmission characteristics of heterogeneous bone structures and the effectiveness of the Monte Carlo in simulating this heterogeneity. These tools provide the capability to develop and optimize treatment plans for optimal release of pharmaceuticals to metastatic breast cancer in the brain.

Results: At the time of these experiments, the voxel-based CUDA MC code implemented and further developed in this study had not been validated by measurement. A novel optical dosimetry probe was fabricated and calibrated to measure the absolute photon fluence (mW/mm²) in phantoms resembling white matter, gray matter and skull bone and compared to 3D Monte Carlo simulated data. The TiO₂-based dosimetry probe was shown to have superior linearity and isotropicity of response to previous Nylon based probes, and was better suited to validate the Monte Carlo using localized 3D measurement (< 25% systematic error for white matter, gray matter and skull bone phantoms along illumination beam axis up to a depth of 2cm in homogeneous tissue and 3.8cm in heterogeneous head phantom). Next, the transport parameters of the empirical algorithm was calibrated using the 3D Monte Carlo and EMs and validated by
optical dosimetry probe measurements (with error of 10.1% for White Matter, 45.1% for Gray Matter and 22.1% for Skull Bone phantoms) along illumination beam axis.

Conclusions: The design and validation of the Monte Carlo, the optical dosimetry probe and the Empirical algorithm increases the clinical feasibility of optical therapeutic planning to narrow down the complex possibilities of illumination conditions, further compounded by the heterogeneous structure of the brain, such as varying skull thicknesses and densities. Our ultimate goal is to design a fast Monte Carlo based optical therapeutic protocol to treat brain metastasis. The voxelated nature of the MC and EM provides the necessary 3D photon distribution to within 25% error to guide future clinical studies involving optically triggered drug release.
1 INTRODUCTION

1.1 Overview

The purpose of our research involves the development of optical dosimetry and simulation tools to quantify and optimize the delivery of light to brain tissues. We start by introducing the concept of optically stimulated drug release for treatment of cancerous lesions in the brain. This mode of therapy requires an efficient optical planning system to determine the best modes of illumination to target tissues in the brain. Such a planning system applies the physics of optical transport to determine the photon distribution in complex heterogeneous media characterized by clinical imaging methods, such as CT and MRI. Critical is the need to validate these methods in tissue phantoms and to determine their accuracy and precision. To realize these ideas into planning systems, which require multiple sources and optimization algorithms, require fast execution times not afforded by MC codes. An Empirical algorithm can achieve these fast simulation speeds. Ultimately, these simulation tools are validated in tissue phantoms using a novel optical dosimetry probe with a Titanium Dioxide with a linear and isotropic response.
1.2 Application in Optically Stimulated Drug Release

To date, brain cancer remains a sanctuary for metastasis. Treatment of Central Nervous System (CNS) metastasis poses a critical clinical challenge due to limitations in drug uptake in the brain (across the blood brain barrier and blood-cerebrospinal fluid barrier) and adverse neurotoxic effects of mainstay therapies, such as whole brain radiation therapy (WBRT) and stereotactic radiosurgery [1-8]. Recently, receptor targeted therapy aided by improved imaging and localized radiotherapy has shown promise in treating cancer within the brain. This is particularly true for HER2+ breast cancer metastasis, which have poor median survival rates of 2 to 16 months [1-7]. Therefore, Dr. Susan Clare, a Surgeon at Northwestern University Robert H Lurie Medical Research Center, devised a method where a patient’s macrophages and monocytes are loaded with a drug payload, in this case a lapatinib laden nanoparticle, to actively delivery and target the metastatic cancer cells. The ‘Trojan Horse’ concept has shown significant promise in targeted drug delivery to the brain, with metastatic cells retaining their sensitivity to the drug even after its administration [8, 9]. The use of macrophages as drug carriers has been proved to be a potentially effective tool because macrophages have been seen to comprise up to 70% of volume in cancerous tumors, such as breast cancer [10-13]. The quantification of macrophages in different tumor types can be done using mouse monoclonal antibody EBM/11 [14, 15], and is an important process in determining the therapeutic accuracy of this potential treatment.
This idea was demonstrated by replacing labeling the payload with fluorescent molecules and showing uptake and fluorescence in brain metastasis of mice, which was published in Cancer Nanotechnology [8, 9]. The long-term goal of this study is to deliver lapatinib-gold nanocomplex laden macrophages to brain metastasis and design a therapeutic protocol to optically stimulate drug release in target tissues in the brain. With the rate and quantity of drug release being directly dependent on the optical power delivered, an optical simulation protocol using Monte Carlo simulations can be designed to effectively predict the photon distribution and subsequent drug activation in the brain tissue.
Figure 1.1 (a) Light-induced release of DAPI (4',6-diamidino-2-phenylindole) within H1299 lung cancer cells. (b) Left: H1299 lung cancer cells containing DAPI prior to illumination and on the right: after NIR exposure. (Input fluence: 1 W/cm², NIR wavelength: 800 nm, 5 minute exposure duration). No major cytotoxicity was observed in assay studies post illumination. (c) Macrophages incubated with gold-silica-nanoshells-red fluorescent microspheres complexes [8, 9]. Intra-cellular accumulation of these fluorescent molecules is seen in the transmission electron micrograph within the cytoplasm vacuoles (see arrow 2). (c) Images using fluorescence microscopy indicate microsphere accumulation through red fluorescence (580/605 nm) [8, 9].
1.3 Applications Requiring Quantification of NIR Light Delivery

While the primary purpose of this research was to enable the quantification of photon propagation in heterogeneous brain tissues, it can be easily applied to NIR based imaging techniques such as Photoacoustic Tomography (PCT), Near Infra-Red Spectroscopy (NIRS) and in optical stimulation of neurons in the brain. The use of the Monte Carlo and the optical dosimetry probe in absolute quantification of photon fluence in tissues can provide the necessary corrections and validation to quantify molecular concentrations in vivo and to deliver the necessary photon dose to trigger therapeutic effects.

Photoacoustic effect involves the absorption of light energy by a molecule, which leads to a thermal heating and volumetric expansion. The generated acoustic wave usually in the ultrasound frequency range is proportional to the optical energy absorbed or dose, and thus a molecule’s concentration such as hemoglobin and injectable dyes. This has led to both clinical and pre-clinical applications such as breast cancer imaging, small animal studies, hemoglobin concentration, oxygen saturation, blood perfusion imaging etc. [16-20]. The application of optical Monte Carlo based methods in Photoacoustic imaging has shown promising results in improving the estimation of photon propagation in complex tissues being imaged [21-26].

Another imaging modality which widely used the penetrating ability of NIR light in tissues, particularly in the brain, is NIR Spectroscopy. The NIR Spectroscopy uses a
source and a detector placed on the surface of the brain. The light gets transmitted through the skull and after undergoing multiple absorption, scattering and refraction events, gets measured by another detector placed on the skull surface near the source. The changes in blood oxygenation in the brain leads to changes in light absorption and can be monitored through the signal detected at various stages of brain activation, initially reported by Jobsis in 1977 [27]. It uses a modified Beer-Lambert’s law for high scattering brain tissues [28, 29]. This technique was initially used to map brain function of cortical tissues in animal and human subjects [30, 31], and later in brain functions of intact skulls in human adults [32-36]. Various applications include monitoring intracellular physiological processes in the brain cells and in measuring Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV) [37-40]. Hence the use of Monte Carlo estimation methods for complex 3D photon propagation along with the optical dosimetry methods can improve the accuracy of the fNRIS measurements by providing absolute quantification of photon fluence.

NIR neural stimulation is another method which requires knowledge of the optical dose in the brain. The use of pulsed infra-red lasers has been shown to trigger the excitation of neurons at a certain optical threshold [41]. This effect has been observed to be wavelength dependent and is seen by measuring the compound action potential (CAP) linked to Ca^{2+} ions in neural mitochondria [41]. Various studies in tissues samples and in-vivo have been carried out to monitor this effect and measure the electrical activity of the brain [42-49]. The use of Monte Carlo methods with wavelength dependent
absorption simulation techniques can provide the necessary information to correlate
the electrical activity in brain tissue, such as the cochlea and neuro-prosthesis.

1.4 Light Transport Theory

The radiative transport equation describes the propagation of light through media and is
considered to be more accurate as it takes into account the absorption and scattering of
light in heterogeneous media [50, 51].

\[
\mathbf{s} \cdot \nabla \mathcal{L}(\mathbf{r}, \mathbf{s}) = -\left( \mu_a + \mu_s \right) \mathcal{L}(\mathbf{r}, \mathbf{s}) + \mu_s \int_{4\pi} \mu(s, s') \mathcal{L}(\mathbf{r}, s') d\omega', \quad (1.1)
\]

where \( \mathcal{L}(\mathbf{r}, \mathbf{s}) \) is the radiance (units: \( \text{W.m}^{-2}.\text{sr}^{-1} \)) at position \( \mathbf{r} \), in the direction \( \mathbf{s} \) (unit vector)
in a medium with an absorption coefficient of \( \mu_a \) and scattering coefficient of \( \mu_s \).

Radiance itself is defined as the radiant flux (Watts/sec) emitted, transmitted or
received by a surface per unit solid angle, per unit projected area [50, 51]. The total
attenuation coefficient (\( \mu_t \)) is the sum of the absorption (\( \mu_a \)) and scattering (\( \mu_s \))
coefficients (units: m\(^{-1}\)). Equation 1.6 describes the change in radiance due to absorption
and scattering out of or into a volume. The differential solid angle \( d\omega' \) is in the direction
of \( s' \) and \( \mu(s, s') \) refers to the phase function, which is the probability of a photon
travelling in direction \( s' \) being scattered into direction \( s \). or characterized by the
parameter \( g \) (anisotropy factor), the cosine average of the phase function:

\[
g = \int_{4\pi} \mu(s, s')(s \cdot s') d\omega'. \quad (1.2)
\]

The value of the parameter \( g \) describes the scattering, for example forward scatter
means \( g=1 \), isotropic scatter by \( g=0 \) and backscatter by \( g=-1 \).
The radiative transport theory assumes a homogeneous distribution of the scattering and absorbing particles in the medium. This assumption and the quantification of the scattering and absorption coefficients can help predict the fluence distribution and the absorbed energy in the medium. There are several approximations to solving the transport equation depending on the type of irradiance (e.g. diffuse or collimated) and optical boundary conditions [50, 51]. For depths far from the light source, there are two solutions which account for un-scattered transmission and an asymptotic fluence-rate: the Beer Lambert’s law and the Diffusion approximation. The Beer Lambert’s law describes the transmission of light through a non-scattering medium:

\[ T = e^{-\mu_t}, \quad (1.3) \]

where \( t \) is the thickness or path-length, \( T \) is the fraction of the intensity transmitted through the medium and \( \mu_t \) is the total attenuation coefficient.

A further modification of the Beer’s Law is made to account for two scattered components [51]:

\[ L(r, s) = L_c(r, s) + L_d(r, s), \quad (1.4) \]

where \( L_c \) is the light that did not interact with tissue while \( L_d \) is the part that underwent scattering. Thus using this diffuse theory approximation in the RTE equation, the fluence can be simplified to [51]:

\[ \varphi(r) = \int_{4\pi} L_d(r, s)d\omega. \quad (1.5) \]
The diffuse approximation is affected by the ratio of scattering-to-absorption coefficients, the tissue distance from the light source, the boundaries and the anisotropy factor [52]. A phase function compatible with the diffusion equation is the Henyey-Greenstein function \( p_{HG} \) [53, 54]:

\[
p_{HG}(s, s') = \left( \frac{1}{4\pi} \right) \sum_{n=0}^{\infty}(2n + 1)g^n P_n(s, s'),
\]

where \( P_n \) are the Legendre polynomials. The phase function given by the delta-Eddington approximation, combines both the diffusion and forward scatter terms, and is given by [55]:

\[
p(s, s') = f \delta(s - s') + (1 - f)p_1(s, s'),
\]

where \( f \) is the forward scatter amount and \( p_1 \) are the first two terms of the Legendre polynomial. The delta-Eddington phase function makes use of the Henyey-Greenstein phase function and is found to be ideal for light propagation in tissues. This is done by the following substitutions [53, 55]:

\[
\frac{g_{HG}}{1 + g_{HG}} = g \quad (1.8)
\]

\[
\mu_s(1 - g^2_{HG}) = \mu_s^1 \quad (1.9)
\]

Thus, the total fluence rate in a material of finite depth is [56]

\[
\varphi(z) = a_1 \exp(kz) + a_2 \exp(-kz) + a_3 \exp(-\mu tz),
\]

where \( z \) is the depth and \( k \) is approximately equal to \( \mu_{\text{eff}} \). This condition is valid only if the absorption coefficient is significantly lower than the scattering coefficient. As per the diffusion theory, the transmittance \( T \) and reflectance \( R \) are given by [57 - 60]:
The optical properties (scattering coefficient ($\mu_s$), absorption coefficient ($\mu_a$), anisotropy factor ($g$)) can be calculated using the total reflectance and transmission. The reduced scattering coefficient ($\mu_s'$) is related to the scattering coefficient ($\mu_s$) as follows [61, 62]:

$$\mu_s' = (1 - g)\mu_s$$  \hspace{1cm} (1.13)

For complex heterogeneous tissues, the relation between reflectance, transmission and the three optical parameters become complicated. A unique computation method used to simulate the random walk of photons across complex heterogeneous media is the Monte Carlo based on $\mu_a$, $\mu_s$, $g$, $n$, and $p(s,s')$

1.5 A GPU based 3D Monte Carlo for photon transport

The Monte Carlo model uses a random number generator to simulate the transport of photons in optical media [57-60] based on the absorption coefficient ($\mu_a$), scattering coefficient ($\mu_s$), anisotropy factor ($g$) and the index of refraction ($n$). A 3D voxel based Monte Carlo allows simulation of complex geometrical boundaries, with each voxel having unique optical properties ($\mu_a$, $\mu_s$, $g$, $n$) [59] A packet of photons is assigned an initial weight and direction, and propagate from one voxel to another, while depositing
energy in each voxel based on its absorption coefficient. The photons also scatter within voxels after travelling a pre-determined distance based on the scattering coefficient of the medium. The new direction of the scattered photon is determined by the anisotropy factor (g) which is the cosine of the phase function [57]. Finally, when the weight of the photon reaches a pre-determined threshold, it is extinguished. The weights deposited by all the photons in each voxel are accumulated to determine the energy deposited, while the total number of photons passing through the voxel is its fluence rate (photons/mm².s) [61].

Traditional CPU based Monte Carlo models [57, 59] suffer from slow computation speeds, which makes them non-viable for application in clinical settings, especially in highly scattering tissues, such as white matter. The GPU based 3D Monte Carlo code used in these studies was shown to be 300X faster compared to our previous CPU based models [61]. The CUDA acceleration provided by this model helps to achieve complete brain simulation of a high fluence broad beam source within hours, as compared to days of simulation time using CPU based models [61 - 63]. This model also provides a voxel based 3D distribution of photon fluence and energy deposited, and can be coregistered with different medical imaging modalities (e.g. CT, MR, Ultrasound, etc.), thus improving its clinical viability for diagnosis and therapy [62, 63].
1.6 An Empirical Photon Propagation Algorithm

While Monte Carlo is the gold standard for photon propagation, it has long execution times even with the acceleration provided by the GPU based models. For high scattering tissues, such as white matter and skull bone, the simulation time for a broad beam simulation is on the order of several hours (based on beam diameter) in order to achieve statistically significant results at depths of more than 2cm [63, 64]. Thus for applications involving optical illumination planning for therapy, where multiple simulations are required for optimizing light delivery to tissues at 5-8cm in depth with complex geometry and heterogeneity, a fast alternate approach is required, particularly for protocols requiring multiple beams [63]. We therefore designed an algorithm based on an empirical model (EM) that simulates photon propagation in heterogeneous voxelated optical media [63, 64].

The EM algorithm implements a convolution technique where the photon fluence within a voxel is the sum of the weighted fluence in neighboring voxels. It simulates photon scatter by assigning weights for forward, diagonal, side and back scatter directions [64]. The fluence within a voxel is assumed to be made of directional components in the x, y, and z directions to emulate the Henyey-Greenstein function. The fluence entering a voxel is redistributed into these directional components such that the sum of the weights is conserved prior to absorption. The scatter weights are determined by comparing the photon fluence distribution with the Monte Carlo under similar
illumination and boundary conditions, before being applied to complex heterogeneous media [64].

The Empirical algorithm provides a fast approach to simulate complete 3D simulations at a fraction of the time (seconds) compared to the Monte Carlo (hours) in complex 3D media (e.g. brain) [63, 64]. This allows us to evaluate multiple illumination conditions for an optical therapeutic protocol for optimized light delivery to tissues within clinically relevant time frames. The 3D voxel based empirical approach also allows for easy integration of the simulated photon energy dose maps with existing imaging modalities, e.g., CT, MR, Ultrasound, Photoacoustic Computed Tomography, which improves therapeutic planning accuracy [63]. Thus the empirical approach can be used a preliminary tool to narrow down the possible illumination conditions, while the Monte Carlo can be used to finalize and quantify the estimated fluence for optical therapy. This makes the use of optical simulation techniques more attractive in clinical settings by reducing the simulation times involved, and is a core purpose of our research.

1.7 A Titanium Dioxide based Optical Dosimetry Probe

Optical dosimetry involves measuring the localized photon fluence in media such as tissues or tissue phantoms. An optical dosimetry probe is a device which consists of a bulb of highly scattering material attached to the exposed tip of an optical fiber, with the other end of the fiber is connected to a photodiode circuit which is in turn connected to an oscilloscope. The light is conducted by the optical fiber to the PIN
photodiode where it is converted into an electrical signal. The dosimetry probe is preferred over calorimeters due to the smaller size, higher sensitivity, and isotropic response of the probe in an aqueous (or liquid) media. In this study, we fabricated an optical dosimetry probe with better isotropicity and locality compared to previous designs of Nylon based probes. The dosimetry probe was used to validate the fluence generated by the Monte Carlo simulation in homogeneous and heterogeneous brain-tissue phantoms. The optical sensitivity of the probe enabled us to validate extremely low fluence in tissue phantoms, unlike the calorimeter.
In Chapter 1, quantifying the photon fluence within a heterogeneous tissue is important for applications including controlled drug release, neuro-stimulation and therapy, and molecular imaging. In each of these applications, quantification of the photon fluence and optical dosimetry is critical. Thus, the focus of this research is on the development of image-based simulation tools to predict 3D photon distributions within optically heterogeneous media and in the advancement of instrumentation to validate these techniques. To accomplish these tasks, we propose to:

**SA1:** Develop, build and test an optical dosimetry probe and advance 3D Monte Carlo photon transport code capable of measuring and simulating the local photon fluence and dose in optical tissue phantoms;

**SA2:** Simulate and validate the absolute photon fluence in homogeneous and heterogeneous brain tissue phantoms resembling white matter, gray matter, skull bone and tumor;
SA3: Devise an empirical model and algorithms capable of simulating for photon propagation in complex heterogeneous tissues in real-time; and

SA4: Investigate the feasibility of using the above tools and methods to optimize optical therapeutic protocols in human skull bones using image-guided techniques.

2.1 Specific Aim1: Develop, build and test an optical dosimetry probe and advance 3D Monte Carlo photon transport code capable of measuring and simulating the local photon fluence and dose in optical tissue phantoms

The rate and quantity of drug release depends on the optical fluence or laser energy delivered to the tissues. To measure the photon fluence being delivered, we have designed and calibrated an optical dosimetry probe to measure the localized (1mm³) photon fluence in tissues with complex optical heterogeneities at depths in brain tissue phantoms consistent with preclinical and clinical applications. Next, CUDA based 3D Monte Carlo code was further developed to predictor of light fluence/energy distribution in tissues. This software has been developed as an open source project by the Dr. Fang’s group at Harvard. We have further modified this software package to model and simulate 3D photon beams with Gaussian and super-Gaussian distributions consistent with the laser beam in our laboratory, along with modifications to increase the computation speed.
2.2 Specific Aim2: Simulate and validate the absolute photon fluence in homogenous and heterogeneous brain tissue phantoms resembling white matter, gray matter, skull bone and tumor.

In order to be used as a therapy planning tool, the 3D Monte Carlo needs to be validated in optical phantoms resembling white matter, gray matter and skull bone. The CUDA based MC code was used to generate 3D photon fluence and energy absorption (or dosimetry) maps generated and validated by optical dosimetry probe measurements in homogeneous and heterogeneous brain tissue phantoms. Since the quantity and energy threshold of drug released depends on the optical energy coupled to the tissues, the cross validation of the dosimetry and simulation tools is a major step in ensuring planning accuracy in clinical setting.

2.3 Specific Aim3: Devise an empirical model and algorithms capable of simulating for photon propagation in complex heterogeneous tissues in real-time

Empirical models of photon transport provide an estimate of the local photon fluence in heterogeneous tissues with fast execution times for the optimization of clinical applications not afforded by Monte Carlo methods. The GPU based Monte Carlo requires many hours of execution time to simulate photon distribution within a human brain, which can be a disadvantage when optimizing a treatment plan iterating over multiple illumination conditions. A weights-based empirical model approach to photon propagation is investigated. It simulates photon scatter by using weights for directional scatter of photons between neighboring voxels, and absorption using the Beer-
Lambert’s law. These weights are determined using the Monte Carlo. The objective is to achieve execution times on the order of seconds. Thus the empirical approach provides an alternative means of evaluating multiple illumination conditions to reduce treatment planning time before using the Monte Carlo for final validation of photon fluence and provide real-time imaging corrections.

2.4 Specific Aim4: Investigate the feasibility of using the above tools and methods to optimize optical therapeutic protocols in human skull bones using image-guided techniques

While dosimetry and simulation studies using optical phantoms helps us measure of the photon distribution in brain tissues under ideal conditions, it does not take into account the heterogeneous composition of the skull bone and the bone-tissue interface, which affects the optical transmission and distribution of photon fluence within the soft tissues. Computed Tomographic images will be acquired to map the density and composition of the bone along with the boundary conditions and to correlate and predict the transmission of NIR light through the skull. Experiments will be performed on human skull bone samples by mapping out the photon fluence transmitted through the bone using the dosimetry probe and comparing it to the Monte Carlo simulated photon distribution. Previous studies have indicated a wide variance in the optical properties of the human skull bone, which can be accounted for by the Monte Carlo code and optical dosimetry probe measurements developed in this research. Thus, the best set of properties for the skull bone for each individual patient can be planned.
3 SPECIFIC AIM1: OPTICAL SIMULATION AND DOSIMETRY TOOLS

3.1 Introduction

In order to estimate the amount of drug released in tissues, we need to be able to derive the number of photons travelling in each voxel (also known as the “fluence”, photons/mm$^2$) and the photon energy absorbed per unit volume (mJ/mm$^3$). The photon fluence maps can be converted into their corresponding drug release maps by using a threshold determined by in vitro studies. We modified a GPU based 3D Monte Carlo (MC) to determine the photon fluence in tissues using different illumination beam profiles. The validation of the MC software in tissue phantoms requires localized measurements of photon fluence in tissue phantoms implementing an optical dosimetry probe with isotropic acceptance. In this chapter, we describe the design, fabrication and calibration of the probe and the validation of the Monte Carlo through its use.

3.1.1 Monte Carlo Algorithm

The Monte Carlo method generates a random number between 0 and 1 with a normal distribution [57] to determine the step size and photon scatter direction based on the optical properties of the medium [57, 59, 61, 64, 65].
The fluence $F(\mathbf{r}, t)$ (mm$^{-2}$s$^{-1}$ or J.mm$^{-2}$s$^{-1}$) in a voxel depends on the raw probability of photon accumulation in a voxel while preserving energy conservation [58]:

$$F(\mathbf{r}, t) = \frac{P(\mathbf{r}, t)E_a/E_t}{\sum_i \sum_j P(\mathbf{r}, t, j) \mu_a(\mathbf{r}, t) \Delta V \Delta t} \quad (3.1)$$
where the raw probability is \( P(\vec{r}, t) \) at a position defined by \( \vec{r} \) and at time \( t \). \( E_a/E_i \) is the ratio of energy absorbed to the total energy in the time interval ("time gate") of \( \Delta t \) and \( \mu_a \) is the absorption coefficient (mm\(^{-1}\)) [61]. The random number \( \varepsilon \) generated between 0 and 1 determines the step size or propagation distance of the photon packet between interactions, \( S_1 \), coefficient (\( \mu_i \)) given by [57, 59]:

\[
S_1 = -\ln(\varepsilon) / \mu_t \quad (3.2)
\]

which depends on the total attenuation:

\[
\mu_t = \mu_a + \mu_s \quad (3.3)
\]

In the above equation, \( \mu_a \) is the absorption coefficient (mm\(^{-1}\)) and \( \mu_s \) is the scattering coefficient (mm\(^{-1}\)). The weight of the photon packet is absorbed within a voxel through which it moves based on the pathlength [57, 59, 61]:

\[
\Delta w = w \left( \frac{\mu_s}{\mu_t} \right) \quad (3.4)
\]

Here the weight lost by the photon packet (with initial weight \( w \)) is \( \Delta w \) and the photon exiting the voxel now has a weight of \( w - \Delta w \).

The step size is calculated each time a photon enters a new voxel with different optical properties. At each interaction site, the new scattering angle (deflection angle) is computed using the cosine of the scattering angle \( \Theta \) [57] based on the Henyey-Greenstein scattering function:

\[
\cos(\Theta) = \frac{1}{2g} \left( 1 + g^2 - \left[ \frac{1-g^2}{1+2g\varepsilon} \right]^2 \right) \quad \text{if } g \neq 0 \quad (3.5)
\]

\[
\cos(\Theta) = 2\varepsilon - 1 \quad \text{if } g = 0 \quad (3.6)
\]
The anisotropy factor $g$ is the cosine of the phase function with values lying in between -1 to 1 [57], where $g=1$ indicates forward scatter, $g=-1$ implies back scatter, and $g=0$ means isotropic scatter. The unit vector directions in the x, y and z axis are as follows [57]:

\[
\mu'_x = \frac{\sin(\theta (\mu_x \mu_z \cos \psi - \mu_y \sin \psi))}{\sqrt{1 - \mu_x^2 + \mu_x \cos \theta}} \quad (3.7)
\]

\[
\mu'_y = \frac{\sin(\theta (\mu_y \mu_z \cos \psi - \mu_x \sin \psi))}{\sqrt{1 - \mu_y^2 + \mu_y \cos \theta}} \quad (3.8)
\]

\[
\mu'_z = -\frac{\sin(\theta \cos \psi)}{\sqrt{1 - \mu_z^2 + \mu_z \cos \theta}} \quad (3.9)
\]

Where $\mu_x, \mu_y, \mu_z$ are the initial (pre-scatter) directional vectors in the x, y, z directions, while $\mu'_x, \mu'_y, \mu'_z$ are the new or post-scatter directional vectors. Also the azimuthal angle $\psi$ (range: 0 to $2\pi$) determines the scattering direction and is given by [57]:

\[
\psi = 2\pi \epsilon \quad (3.10)
\]

The Monte Carlo code takes the anisotropy factor along with the values of the index of refraction, absorption and scattering coefficients as an input from the user to define the optical properties of the medium. The photon energy deposited (or dose) ($E_{abs}$ in photons or Joules) in each voxel is given by the product of the photon fluence ($F(\bar{r}, t)$ in mm$^{-2}$s or J mm$^{-2}$s), the absorption coefficient ($\mu_a$ in mm$^{-1}$), the photon pulse duration (or illumination time) ($t_{int}$ in s) and the volume of the voxel ($v_{vol}$ in mm$^3$):

\[
E_{abs} = F(\bar{r}, t) \mu_a t_{int} v_{vol} \quad (3.11)
\]
3.1.2 Optical Dosimetry Probe

The optical dosimetry probe consists of an optical fiber, with its exposed end inside a spherical bulb made of a highly scattering material (e.g. Arnite, Nylon or Titanium Dioxide). The other end of the fiber was optically coupled to a PIN photodiode circuit [68, 69]. The light entering the spherical tip causes the light to scatter in all directions so the fraction entering the fiber from any direction is the same. Some of the photons enter the optical fiber tip while others escape back into the surrounding medium. The difference in the refractive index of the TiO2-epoxy sphere and the surrounding medium determines the number of photons which escape back into the medium, which in turn determines the probe’s response or sensitivity [68]. The photons entering the optical fiber are conducted to the PIN photodiode circuit which converts the incident photons into a corresponding voltage signal, which is shown to be proportional to the light
exposed to the TiO2-sphere [63, 68, 69]. This electrical voltage is then read using a
digital oscilloscope and integrated to obtain a quantifiable measure of the optical
fluence [63].

The radiant energy fluence rate at a position “r” is the integral of radiance $L(r, \hat{s})$ (units
Wsr$^{-1}$m$^{-2}$) over all directions (defined by solid angle "$\Omega$") and is given by [68]:

$$\psi(r) = \int_{4\pi} L(r, \hat{s})d\Omega$$  \hspace{1cm} (3.12)

where the solid angle about the normal vector $\hat{s}$ is $d\Omega$.

The optimal construction of the dosimetry probe is such that the optical fiber is inserted
a predefined distance within the TiO2 sphere. This prevents a part of the light fluence
within the probe tip from entering the fiber, thus creating a “blind spot” [68]. This
requires a correction factor to be applied to the 4$\pi$ sr solid angle acceptance of an ideal
dosimetry probe (without a blind spot). The blind spot can be defined in terms of the
solid angle $\Omega_{\text{blind}}$. This correction factor $F_b$ in a probe with fiber diameter $d$ and diameter
$D$ of the TiO2 sphere (with "$\theta$" as the arbitrary angles of incidence) is given by [68]:

$$F_b = \frac{\Omega_{\text{sphere}}}{\Omega_{\text{sphere}} - \Omega_{\text{blind}}} = \frac{4\pi}{4\pi - 2\pi \int_0^{\arcsin\left(\frac{d}{D}\right)} \sin \theta d\theta} = \frac{2}{1 + \cos[\arcsin\left(\frac{d}{D}\right)]]}$$  \hspace{1cm} (3.13)

Thus,

$$F_b \approx 1 + \frac{d^2}{4D^2}$$  \hspace{1cm} (3.14)

The fluence passing through the fiber is measured by a flat PIN photodiode, whose
response $S_{\text{flat}}$ is given by [68]:
Similarly, for a dosimetry probe, infinitely small, the response to diffuse isotropic fluence is given as [68]:

$$S_{point} = \int_{2\pi} L_0 \cos\theta \, d\Omega = 4\pi L_0 \int_{0}^{\pi/2} \sin\theta \, d\theta = 4\pi L_0 \quad (3.16)$$

Thus in order to obtain the true fluence rate entering the probe, we multiply the response of the PIN photodiode by a factor of 4, given by [68]:

$$\frac{S_{flat}}{S_{point}} = \frac{\pi L_0}{4\pi L_0} = \frac{1}{4} \quad (3.17)$$

Similar to the blind-spot factor, a correction factor accounting for the difference in the refractive index of the probe tip and the medium must be applied. The ratio of the response of the dosimetry probe in liquids ($F_n$) relative to air has been studied and measured extensively [68] and depends on the difference in the index of refraction between the medium and the probe tip. The greater the difference in the refractive indices causes a higher fraction of photons to be refracted back into the probe, and higher sensitivity, compared to lower differences, e.g. TiO2-epoxy to air versus water. The refractive index of the probe (solid) is well above the refractive index of water, thus measurements in liquids with higher refractive index gives higher probe sensitivity.

Another potential correction factor, $F_i$, accounts for inhomogeneity in the construction of the spherical probe tip resulting in an anisotropic response [68]. This factor accounts for the angular variance in the probe’s response to different incidence angles in the
equatorial and azimuthal directions. Excluding the extreme blind spot at oblique angles (i.e. from the same direction as where the fiber enters the spherical bulb), the angular variance of a well-constructed probe is generally low [63, 70]. In this study, the angular response of the dosimetry probes to diffuse incidence fluence was measured to determine its isotropicity of response. Thus the reading in air must be corrected to obtain the true fluence rate ($\psi_m$) using the following equation [68]:

$$\psi_m = \psi_{air} F_n F_b F_i$$  (3.18)

3.2 Materials and Methods

3.2.1 Monte Carlo Beam Optimization

The original code of the GPU based 3D Monte Carlo (MC) (by the Fang group [61]) has several built-in features to simulate photon sources such as Gaussian, flat beams, pencil beams, isotropic point sources, cone beams, etc. The “open source” availability of this software and functionality of using random numbers to generate and define photon sources allows users to modify the original source code to add additional photon beam profiles as used in different optical setups. The CUDA based parallel threading functionality also improves the speed of simulation of broad beam sources compared to the time consuming nature of simulating multiple pencil beams by calling Monte Carlo function separately for each pencil beam. Even though we had used the process of generating broad beam profiles, by calling the Monte Carlo serially, in our past studies [60]; in this study we have optimized the Monte Carlo to generate broad beams by using
the full functionality of the CUDA platform by generating individual pencil beams in parallel.

In this study, we modified the original code to simulate a broad beam super-Gaussian beam profile emanating from an optical fiberguide, coupled to the output of a Laser-OPO system (Nd: YAG class 4 laser and a MagicPRISM Optical Parametric Oscillator from Opotek Inc., Carlsbad, CA). This profile was measured with a calorimeter (gold standard) (Ophir-Spiricon 3A-P-V1) with aperture 12mm, and can be represented with the following equation:

\[
\Phi_{\text{superGaussian}} = A \times e^{0.5 \left( \frac{r}{\sigma} \right)^n} \tag{3.19}
\]

where:

\[
r = z \tan \theta \tag{3.20}
\]

In the above equations, \( A \) is the maximum or peak incident energy fluence (J/mm\(^2\)), \( z \) is the perpendicular distance from the source to a point along the central axis of the beam, \( \theta \) is the divergence angle of the laser beam, \( \sigma \) is the standard deviation of the super-Gaussian lateral beam profile, \( n \) is the order of the super-Gaussian distribution. The broad beam output of the fiberguide was approximated using multiple single sources with super-Gaussian outputs. In our experimental setup, a match in beam profile was obtained for \( \sigma=3.8 \) and \( n=2.9 \). The radius of the fiberguide source is 0.3cm. Besides the super-Gaussian beam from the fiberguide, a flat broad beam with radius equal to the output port of the integrating sphere (port radius 0.9cm) was used to characterize the
output of the integrating sphere. The beam characteristics were measured using a calorimeter (gold standard) and were given as input to the MC code to emulate the illumination conditions used in the optical dosimetry setup.

We also added additional functionalities to the Monte Carlo to emit broad beam profiles such as converging and diverging beams as emitted when light beams pass through convex and concave lenses. This is of particular importance to researchers who wish to explore the effect of different beam profiles on photon energy distribution in tissues.

In order to implement the simulation of converging and diverging beams, we allow the user to select the beam parameters such as the aperture size (radius) and focal distance, e.g., the real or virtual focal length for converging or diverging beams, respectively.

In order to simulate converging and diverging beams, we need to define the angle of the photon source vector for each individual pencil beam. We define the emission angle $\theta$ for a beamlet as:

$$\theta = \tan^{-1}\left(\frac{r}{f}\right) \quad (3.21)$$

where $f$ is the focal depth and $r$ is the radial distance from the center of the aperture of the point source (or do you mean beamlet). The parameter $r$ is selected randomly from 0 to $R$, where $R$ is the radius of the source aperture. The angle of the photon beamlet from this point within the aperture is $\left(\frac{\pi}{2} - \theta\right)$. For a converging beam the initial photon
vector is defined by $-\sin(\theta)$ and $-\cos(\theta)$ and for the diverging beam this vector is defined by $\sin(\theta)$ and $\cos(\theta)$. The equatorial angle ($\Phi$) is randomly chosen from 0 to $2\pi$. The photon vector directions are then calculated using equations 3.6, 3.7 and 3.8.

3.2.2 Optical Dosimetry Probe Design and Calibration

Two models optical dosimetry probes constructed with Nylon and Titanium Dioxide spherical tips were fabricated and compared, specifically their sensitivity and isotropicity of response.

The Nylon spheres have been widely used for photodynamic therapy and were made of Nylon\textsuperscript{TM} due to their isotropic response [26]. These were used as the standard of reference to compare the performance of Titanium based probes. TiO$_2$ probes are made from a mixture titanium dioxide (Du Pont Ti-Pure R-900) and a clear two-part epoxy (Tra-Con BA-F114) in a ratio of 9.1 mg TiO$_2$ to 1 ml of the epoxy [28, 29]. Titanium dioxide was selected due to its particle size of around 410nm [28], which results in optimal scattering at 820nm, the wavelength is approximately twice the particle size [28] and in the center of the NIR spectrum (700-920nm). Since the wavelength used in our studies is 800nm, the titanium probes have been designed to show a higher sensitivity than the Nylon probes. The titanium based probe tips were fabricated using a specially designed mold [70]. A fiber optic cable (BFL48-400, 4mm diameter, 0.48 numerical aperture) was inserted within the cured spheres at a depth of approximately 1/3 of the sphere’s radius [72]. The Nylon based probes were approximately 3.175mm diameter.
and were machined in a multistage process [70]. The other end of the fiber optic cable was connected to PIN photodiode (ET-2030, Electro Optics Technology Inc.) though a SMA-905 connector and the voltage output was read using a digital oscilloscope (Tektronix TDS3052B).

![Diagram of optical dosimetry probe](image)

**Figure 3.3 Setup for calibration of the Optical dosimetry probe: measuring isotropicity (in equatorial and azimuthal planes) of the probe**

First, the isotropic response of the probe was measured. The experimental setup shown in Figure 3.3 was used to measure the probe’s equatorial and azimuthal response. The
probe is mounted on and rotated by a rotary stepper motor, while keeping the same central location of the probe. At each equatorial and azimuthal angle, the probe is illuminated by a uniform broad beam of diffuse light formed by laser light (800 nm) emanating from an integrating sphere (Melles Griot two port integrating sphere) and its response, the output rms voltage, was measured at each angle. The isotropicity is measured by calculating the coefficient of variation, the ratio of standard deviation to mean of the rms value over all the angles. The range of angles was 0 to 360 degrees for equatorial measurements, and 0 to 150 degrees for azimuthal. The angular span for Azimuthal measurements was limited due to physical limitations of the setup which prevented larger angles due to presence of the integrating sphere. The individual rms voltage measured by the probe was normalized to the power measured using a calorimeter.
Figure 3.4 Setup for calibration of the Optical dosimetry probe: measuring the linearity of the probe to incident laser fluence.

Second, experiments were performed to measure the linearity and sensitivity of the probe (figure 3.4), and calibrate the dosimetry probe response to calorimeter (Ophir CE, [Nova 2 Ophir: 3A-P-SH-VI], aperture 12 mm). The probe was illuminated with a pulsed laser beam (800 nm; 10 Hz repetition rate) with an output of 10.2 mW/cm² fluence rate and total output energy of 0.02 J/pulse. The probe and the calorimeter are translated along the beam axis (in air) and the photon fluence is measured at different positions. The integrated voltage normalized to the exposed area of the probe ($\Phi_{\text{probe}}$, mV/mm²) was plotted as a function of calorimeter measurements ($\Phi_{\text{calorimeter}}$, mW/mm²) and fitted to a line.

$$\Phi_{\text{probe}} = \frac{\Phi_{\text{calorimeter}} + 1.7296}{590.46} \quad (3.22)$$
Note that the probe voltage signal was filtered using a bandpass Butterworth filter to remove high frequency noise in the probe response. The photon fluence is proportional to integral of the probe voltage output over the time of the laser pulsed. The probe’s integral voltage as well as the calorimeter power was normalized to the exposed surface areas of these detectors, where the probe (spherical) surface area is 7.065mm² and the calorimeter (circle) surface area of 113.04mm².

The linear relationship in equation 3.19, used to quantify the photon dose in air, was modified to account for the optical fluence in liquid brain phantoms. The light entering the dosimetry probe depends on the ratio of the refractive index of the TiO2-expoxy sphere to the medium. The refractive index of probe tip lies between the refractive indices of titanium dioxide (approximately 2.73) [29] while that of the epoxy (around 1.53). Since the refractive index of air is smaller than that of water, the probe response in water is smaller as more light will escape the probe when placed in water. The reflectance factor is 0.41 for the probe-to-air interface (n_{probe}/n_{air} is 2.5), and 0.74 for the probe-to-water (n_{probe}/n_{water} is 1.88) [26]. The difference in the refractive index and reflectance between probe-air and probe-water interfaces (water and tissue have similar refractive index of 1.329) must be accounted for to quantify photon dose in water. In order to determine the calibration factor, we measured the probe response in air and water within a cuvette illuminated by a diffuse broad uniform beam emanating from an integrating sphere (same setup as figure 3). The probe was placed inside the cuvette, 0.2cm from the surface. First the probe response was measured in air (\(\phi_{air}\)) and
then measured again by filling the cuvette with water ($\phi_{\text{water}}$), without changing the position of the probe with respect to the cuvette and the laser source. By accounting for the water attenuation ($\mu_{\text{water}}$ of 0.02 cm$^{-1}$ and a path length of 0.2 cm) and the difference in the beam spread due to change in refractive index, the calibration factor (CF) was determined experimentally to be 1.318, using the following equation:

$$CF = \frac{\Phi_{\text{air}} \left( e^{-\mu_{\text{water}} s} \right) \left( \frac{\text{fwhm}_{\text{air}}}{\text{fwhm}_{\text{water}}} \right)}{\phi_{\text{water}}}$$ (3.23)

The difference in the beam spread difference between the cuvette-air setup versus the cuvette-water setup is accounted for by multiplying the fluence measured in air with the ratio of the measured beam spreads: fwhm$_{\text{air}}$=40 mm and fwhm$_{\text{water}}$=42 mm, or a ratio of 0.9091. The experimentally derived calibration factor is then used for absolute photon quantification by multiplying it to the probe response measured within tissues and tissue-like media as follows (from equation 1 and 2):

$$\Phi_{\text{absolute}} = \frac{(CF \Phi_{\text{tissue}}) + 1.7296}{590.46}$$ (3.24)

where $\phi_{\text{absolute}}$ is the absolute dose in mW/mm$^2$ and $\phi_{\text{tissue}}$ is the probe response (mV/mm$^2$), which is proportional to fluence measured in the tissue over the surface area of the probe.
3.3 Results

3.3.1 Monte Carlo Optimization

The Monte Carlo software was modified to simulate a super-Gaussian beam profile by generated by laser light passing through an optical fiberguide. Figure 3.5 shows the lateral fluence profiles generated by the MC and that measured by the calorimeter. Modifications were also done to the original MCX software to simulate converging and diverging beams, which are shown in figures 3.6 and 3.7. These were added for future analysis of complex beam setups with lenses of specified focal length and numerical aperture.

![Beam Profile in Air (MC v/s Calorimeter)](image)

Figure 3.5 Super-Gaussian beam generated by the Monte Carlo, compared with the optical fluence measured using a calorimeter [63].
Figure 3.6 Images of converging, diverging and flat beams generated by the Monte Carlo.

Figure 3.7 shows an MC simulation of three convex lenses with different focal lengths and with an aperture of 5mm. The increase in focal distance leads to a widening of the focal spot in the z-direction as expected.

3.3.2 Optical Probe Calibration

The optical dosimetry probe was designed to quantify the localized fluence distribution in tissues with a high degree of accuracy. This design was compared with standard probes made from Nylon in order to analyze the advantages in linearity and anisotropy of the novel probe model. The probe response was then characterized to quantify the absolute photon fluence in tissues. This procedure involved the use of filtering to reduce the statistical noise in the probe voltage and the determination of probe characteristics in water (with tissue equivalent refractive index) versus those in air.
Figure 3.7 Simulation plots of converging beams along beam axis in water. Three converging beams were simulated with the same aperture size (radius 5mm) and with different focal depths (15mm, 25mm, 55mm). The larger focal depths show a broader distribution of photon fluence (along the beam axis) with increase in focal depth.

The isotropicity (coefficient of variation) of Nylon and Titanium based optical dosimetry probes are shown in figure 3.8. The titanium based probes showed a better isotropicity with an equatorial coefficient of variation 0.0386 versus 0.1929 for Nylon probes and an azimuthal coefficient of variation of 0.216 for titanium versus 0.441 for Nylon. A titanium based probe with a 1.5mm diameter was selected for further dosimetric studies and had an equatorial coefficient of variation of 0.0721 and an azimuthal coefficient of variation 0.2959.
Figure 3.8 Probe isotropy of Titanium vs Nylon probes. The coefficient of variation (standard deviation/average rms voltage) was calculated for probes made of Nylon and Titanium. The error bars show the minimum and maximum values of variation in individual probe response. The Titanium based probes showed a more isotropic response in the equatorial and azimuthal directions. A 1.5mm diameter Titanium probe was selected for further dosimetric studies.

Figure 3.9 shows the linearity of response of the 1.5mm Titanium based probe. The probe response is linear over a dynamic range of 0.01074mW/mm² to 0.031316mW/mm² as measured by the calorimeter. The standard error (Standard Deviation/√n) and percentage error variation in probe response was quantified by measuring multiple probe response in air over distances 10.1 to 18.1cm from the fiberguide surface. The error in probe response is 1.695% (standard error = 0.226) and the % error in calorimeter readings was 1.1299% (standard error = 0.00495). On the other hand, the variation of the laser light emitted from the fiberguide over time was approximately 3%. Thus the error due to variation in pulsed optical power of the laser
was the major source of error in our measurements. These showed that Titanium probes are better suited to optical dosimetry studies, as compared to Nylon probes, and were used in brain phantom studies. While Nylon probes have been used before in dosimetry studies, this is the first time that titanium probes were designed with a better isotropic response.

Figure 3.9 Probe linearity: graph of total voltage (area under pulse) (mV/mm²) measured by a 1.5mm diameter Titanium probe versus the power measured by a calorimeter per unit surface area (mW/mm²). The probe response is linear over a dynamic range of 1.2mW to 3.5mW as measured by the calorimeter. The error bars represent 3% variation in pulsed laser power fluctuation measured by the probe and calorimeter.

The filtering of the probe response reduces the noise in the probe voltage and provides a clean signal. The Butterworth filter used can be tuned to optimize the signal to noise ratio and removes the high frequency noise in the probe voltage, mainly attributed to
electronic noise externally induced in the PIN photodiode circuit. The use of the filtered
signal also reduces the noise dependency of the measured fluence as we saw that the
noise variations in the measured signal mainly affected the measured output in the low
fluence regions, where (S/N) ratio is low. The filtering step (final versus initial signal) is
shown in figure 3.10. It is clearly seen that the high frequency noise at the periphery of
the signal is reduced. This can be even reduced further by adjusting the filter
coefficients, based on the operator’s discretion.

In order to quantify the measured probe voltage, there are several methods which can
be used. Some commonly measured parameters are the root mean square (RMS)
voltage, mean voltage and maximum voltage. In our studies we found that the RMS
voltage is a reliable parameter can be used to quantify the signal. However the RMS
voltage also depends on the signal noise and can be problematic if the noise level
changes with photon fluence measured. Thus in order to quantify the photon fluence,
we used the integral of the voltage (or area under the peak) of the measured signal. This
quantity can be made independent of the noise level by summing only those voltages
above a certain noise threshold level. In our studies, we found that a threshold of 5% of
the maximum value of the measured voltage was sufficiently above the average noise
variations at the signal periphery. Thus, while RMS value is a quick means to estimate
the measured fluence, the area under the peak can be a better measure of the absolute
photon fluence, provided all the necessary calibration factors are calculated.
In order to calculate the absolute photon fluence in tissues and tissue-like media, the probe voltage measured within the medium must be multiplied by the calibration factor to account for the change in photon loss in the probe-medium interface with respect to the probe-air interface, where the calibration was performed. Since the refractive index of tissues is nearly the same as that of water, the calibration factor obtained for water can be used for biological media. The probe calibration factor was determined to be 1.32. The technique presented (using equations 3.22, 3.23, 3.24) provides a simple method to determine the calibration factor experimentally, and is a novel addition to our research. It is important to note that while equation 3.23 remains the same for any probe, the
equations 3.22 needs to experimentally determined, so as to derive equation 3.24 for absolute photon dose quantification.

3.4 Discussion

The Monte Carlo code was optimized to emit a super-Gaussian beam profile. Its voxel based design allows us to clearly define object boundaries and specific optical properties of each voxel in the volume to be simulated, generating a photon fluence (units: $J.mm^{-2}.s^{-1}$ or photons.$mm^{-2}.s^{-1}$) and an absorbed energy (units Joules) map. The latter is calculated by multiplying the simulated fluence ($J.mm^{-2}.s^{-1}$) with the absorption coefficient (units $mm^{-1}$) of the voxel, volume (units: $mm^3$) of the voxel and the length of the time period (units: seconds). The 3D voxelated output of the Monte Carlo is can be conveniently integrated and analyzed with 3D medical imaging modalities such CT, MR, Ultrasound, etc. Thus absolute photon quantification using Monte Carlo has the potential to be used for image guided therapy. The reduction in simulation times (couple of hours) of the CUDA based Monte Carlo also improves its potential to be applied in the clinic for calculating the photon dose in optical based therapies.

We designed an optical dosimetry probe with a linear and isotropic response, and with superior sensitivity compared to Nylon probes. These dosimetry probes can now be used for in vitro and in vivo studies for localized measurement of the absolute photon fluence. The calibration of the dosimetry probes allows us to measure its linearity and isotropicity and derive the calibration factors necessary to measure the absolute energy
fluence in mW/mm². The calibration factor (1.32) derived in this study accounts for the
difference in the sensitivity of the probe in air and water. The other calibration factor is
the isotropic sensitivity of the probe and depends on the probe orientation. This factor
gives the % error in probe response based on the azimuthal and equatorial orientation
of the probe. An average error over all the angles is sufficient to understand the
variations in measurement based on probe orientation, with the goal of having each
measurement independent of the probe’s absolute position in the media. More studies
using goniometric measurements may improve the accuracy of the measurements and
are recommended before using the probe in a clinical setting. Our study has shown the
advantages of using Titanium Dioxide probe over traditional probes made of Nylon for
dosimetry studies for NIR wavelengths of around 800nm. More dosimetry probe
materials can also be researched for better sensitivity at larger infra-red wavelengths if
necessary.
4  SPECIFIC AIM2: VALIDATION OF MONTE CARLO IN TISSUE PHANTOMS

4.1  Introduction

In order to be used as a therapeutic tool, the Monte Carlo software needs to be validated. The Titanium Dioxide based optical dosimetry probe, described in the previous chapter, allows us to accurately measure photon fluence distribution with millimeter resolution, high sensitivity, and negligible orientation dependencies, compared to previous Nylon-based dosimetry probes. In this chapter we describe the design of accurate tissue phantoms of white matter, gray matter, and skull bone used to validate the Monte Carlo generated photon fluence. In all these studies, the optical dosimetry probe serves as a gold standard photon energy fluence and its uncertainty.

4.1.1  Optical Phantom Characteristics

The design of optical phantoms requires an accurate and precise measure of the absorption coefficient ($\mu_a(\lambda)$), scattering coefficient ($\mu_s(\lambda)$) [or reduced scattering coefficient $\mu_s^1(\lambda) = (1-g) \mu_s(\lambda)$], anisotropy factor (g) and refractive index (n), at a wavelength/s of interest ($\lambda$) of the materials used to represent skull bone, white and gray matter. Since tissues are made of molecules which scatter and absorb photons, an optical tissue phantom is composed of a combination of scattering (e.g. Intralipid, Titanium dioxide, Aluminum Oxide, Polymer Microspheres, Quartz Glass Microspheres) and
absorbing materials (e.g. India Ink, Molecular dyes such as Indocyanine Green (ICG), Fluorophores), each in varying proportion based on their individual absorption and scattering properties [73-77]. These absorbers and scatterers are added to water or agar, which provides a stabilizing medium for uniform distribution of the absorber and scatterer molecules, and defines the refractive index of the resulting phantom. An optical phantom should be designed such that its optical properties closely match those of the corresponding tissue at the wavelength of interest. This however is a complex problem due to the apparent mismatch between “non-absorption” related properties ($\mu_a(\lambda)$, g, n) of absorbers and “non-scattering” related properties ($\mu_s(\lambda)$, g, n) of scatterers across different wavelengths ($\lambda$). One way to reduce this complexity is to select materials that have closely matching g and n values to tissue (water and agar), a pure scattering media with negligible absorption properties, and a pure absorber with negligible scattering properties, while allowing uniform mixing of absorber and scatterer molecules [73].

4.1.2 Spectro-photometer Calibration

In this study, intralipid was used as a scatter and India ink as an absorber in concentrations that resemble the optical properties of white matter, gray matter and skull bone. For each tissue type used in the brain phantom, the absorption coefficient of India ink and scattering coefficient of intralipid were determined using a spectro-photometer which served as the gold standard to measure absorption and scattering properties. While absorption properties of India ink (units: %Concentration$^{-1}\text{cm}^{-1}$) vary from batch to batch in commercially available samples, the variation in the scattering properties (units: %Concentration$^{-1}\text{cm}^{-1}$) of Intralipid are less across different samples. This is
mainly due to the fact that intralipid composition is controlled for medical use. Both these properties were validated using a spectro-photometer and calibration curves of $\mu_a(\lambda)$ and $\mu_s(\lambda)$.

![Figure 4.1 Measurement of light transmission in a Spectro-photometer. A fine pencil beam of a specific wavelength is transmitted across a sample contained in a glass cuvette with a fixed path length. The absorbance of the sample is calculated using Beer Lambert’s law [78].](image)

The spectro-photometer measures the transmission of light across samples for specific wavelengths of interest. It uses the Beer Lambert’s law [78] to calculate the absorbance of the medium from the incident light intensity ($I_0$), transmitted light intensity ($I_t$) and optical path length ($x$). For a path length of 1 cm, the absorbance ($A$) (cm$^{-1}$) of a sample is given by [78]:

$$A = \log_{10}\left(\frac{I_0}{I_t}\right) \quad (4.1)$$
For a purely absorbing medium the absorbance measured by the spectrophotometer is related to the absorption coefficient of the medium by:

$$\mu_a(\lambda) = \frac{\log e(\Delta)}{\log e(10)} \quad (4.2)$$

where "log e" is the natural logarithm. Similarly the scattering coefficient of a medium with a low concentration of scatterers can also be derived from the absorbance measurement of the spectro-photometer:

$$\mu_s(\lambda) = \frac{\log e(\Delta)}{\log e(10)} \quad (4.3)$$

Equation 4.3 is true only if the transmitted light intensity is collimated, does not undergo multiple scattering events and if the detector aperture is very small [76]. This places restrictions on the range of concentrations across which the scattering properties can be measured using the spectro-photometer. In this study we validated the scattering properties of the intralipid medium across extremely low concentrations using probe measurements as well as by comparing to past studies. Past studies by Van Staveren [76] have measured the optical properties of intralipid, which can be derived using the equations [76]:

$$\mu_s(\lambda) = 0.016\lambda^{-2.4} \quad (4.4)$$

and

$$g(\lambda) = 1.1 - 0.58\lambda \quad (4.5)$$

where \(\lambda\) is in micrometers (0.4< \(\lambda\) <1.1) and the scattering coefficient \(\mu_s(\lambda)\) is in mL\(^{-1}\).L.mm\(^{-1}\). This yields an anisotropy factor of \(g(\lambda) = 0.636\) and a reduced scattering
coefficient of 9.95 (%Concentration)$^{-1}$cm$^{-1}$ at $\lambda = 800$ nm. In this study we have used the anisotropy factor derived from equation 4.5 and will compare the scattering properties of intralipid to those obtained through equation 4.4.

4.1.3 Probe and Monte Carlo based validation of intralipid

To further verify the optical properties of intralipid solutions, we did another study using the dosimetry probe to measure the extinction coefficient of intralipid solutions. The extinction coefficient derived by the probe measurements were then matched by the Monte Carlo. The corresponding scattering coefficients which showed the best match to data were selected as the true values for that concentration. This additional study cross validates the spectro-photometer studies [76] shown by equation 4.4. The reasoning behind this study was to be absolutely sure that the scattering coefficient per unit volume of the 20% intralipid samples used in our studies were of the same property as the 10% intralipid samples used by the Van Staveren study.

4.2 Materials and Methods

4.2.1 Characterization of Optical Phantoms

Optical brain phantoms were designed to emulate the absorption and reduced scattering coefficients of white matter, gray matter and skull bone at 800nm [79, 80]. Previous studies have shown that reliable optical phantoms can be built using India ink (absorber) and intralipid (scatterer) [74 – 77], in addition to the optical absorption by water molecules ($\mu_a = 0.02$cm$^{-1}$) [81].
The absorption coefficient of India ink (Higgins non water proof black ink) and the scattering coefficient of intralipid (Intralipid 20% from Fresenius Kabi), at 800nm wavelength, was determined and validated using a spectro-photometer (Shimadzu UVmini 1240 Spectrophotometer), which served as the gold standard to measure absorbance. The scattering properties of intralipid can be determined using the spectrophotometer for low concentrations and was found to have the average value of 9.524 cm\(^{-1}\) %Concentration\(^{-1}\), compared to 9.95 cm\(^{-1}\) %Concentration\(^{-1}\) as shown in past studies by Van Staveren [76]. Figures 4.2 and 4.3 show the calibration curves of the absorbance versus concentration of India ink and Intralipid, and the linear fit was used to design optical phantoms that resemble white matter, gray matter and skull bone, similar to Van der Zee [79] and Firbank [80]. In Tables 4.1 and 4.2, the measured ex vivo optical properties (absorption and scattering coefficients and anisotropy factor) of skull bone, gray and white matters and those used in our research studies are shown (the latter derived from figures 4.2 and 4.3).
Figure 4.2 Calibration curve of spectrophotometer measured absorbance versus %Concentration of India ink. The error bars represent minimum and maximum absorbance.
Figure 4.3 Intralipid Scattering: Upper figure represent measured values of scattering coefficients ($\mu_s$ and $\mu_s'$) versus %Concentration of Intralipid using a spectrophotometer. The error bars represent minimum and maximum values. Lower figure shows extrapolated values from the linear relationship derived from the measured values.

Both homogeneous as well as heterogeneous phantoms were made using various concentrations of India ink and Intralipid. The phantom composition for homogeneous phantom was a solution of India ink and intralipid in water, while the heterogeneous
phantoms comprised of layers of 1% agar doped with India ink and intralipid to represent skull bone and gray matter, and topped with a solution of white matter. The agar phantom preparation involved boiling a solution of India ink (with predetermined concentration) and 1% agar (Fisher Scientific Laboratory Grade Agar A3600-500) in a microwave at 95 degree Celsius and adding intralipid to the solution after being stirred and cooled to below 45 degrees Celsius. The scattering properties of agar and absorption properties of India ink were also measured using a spectrophotometer for each individual sample used in the study, while the scattering properties of intralipid were derived from the linear relationship in figure 4.3.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Absorption Coefficient ($\mu_a$) (cm$^{-1}$)</th>
<th>Scattering Coefficient ($\mu_s$) (cm$^{-1}$)</th>
<th>Anisotropy Factor (g)</th>
<th>Reduced Scattering Coefficient ($\mu'_s$) (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter</td>
<td>0.05</td>
<td>550</td>
<td>0.85</td>
<td>82.5</td>
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<tr>
<td>Gray Matter</td>
<td>0.35</td>
<td>700</td>
<td>0.965</td>
<td>24.5</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>0.24</td>
<td>184</td>
<td>0.9</td>
<td>18.4</td>
</tr>
</tbody>
</table>
### Table 4.2 Phantom Composition [63]

<table>
<thead>
<tr>
<th>Phantom Type</th>
<th>Tissue Type</th>
<th>Intra lipid %</th>
<th>Ink %</th>
<th>Absorption Coefficient ($\mu_a$) (cm$^{-1}$)</th>
<th>Scattering Coefficient ($\mu_s$) (cm$^{-1}$)</th>
<th>Anisotropy Factor (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid Phantom</td>
<td>White Matter</td>
<td>7.5</td>
<td>0</td>
<td>0.002</td>
<td>197.352</td>
<td>0.636</td>
</tr>
<tr>
<td>Liquid Phantom</td>
<td>Gray Matter</td>
<td>2.36</td>
<td>0.023</td>
<td>0.3792</td>
<td>62.187</td>
<td>0.636</td>
</tr>
<tr>
<td>Liquid Phantom</td>
<td>Skull Bone</td>
<td>1.82</td>
<td>0.0156</td>
<td>0.26</td>
<td>47.922</td>
<td>0.636</td>
</tr>
<tr>
<td>Solid Phantom</td>
<td>Gray Matter</td>
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<td>0.0195</td>
<td>0.35</td>
<td>67.308</td>
<td>0.636</td>
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<tr>
<td>Solid Phantom</td>
<td>Skull Bone</td>
<td>1.92</td>
<td>0.0134</td>
<td>0.25</td>
<td>50.549</td>
<td>0.636</td>
</tr>
</tbody>
</table>

#### 4.2.2 Validation of 3D Monte Carlo in brain phantoms using Optical dosimetry

As described in the previous section, liquid optical phantoms, resembling white matter, gray matter and skull bone, were designed using predetermined concentrations of India ink and Intralipid. The setup for the light dosimetry in the phantoms is shown in figure 4.4. Two sources of NIR light (an integrating sphere and an optical fiberguide) were used to illuminate the phantoms, both of which were connected to the laser source (same specifications as used in the calibration process). The dosimetry probe was inserted into the phantom and translated using a 3D translation micrometer stage and used to measure the optical fluence distribution at various $x$, $y$ and $z$ locations within the phantom. The $x$, $y$ and $z$ fluence distribution generated by the Monte Carlo was compared to the probe measurements to test the validity and accuracy of the Monte Carlo code. The percentage match of the Monte Carlo was calculated relative to the probe measurements to estimate the level of confidence of fluence estimation. The %
difference between the probe measured fluence and the Monte Carlo was calculated both along and perpendicular to the beam axis.

Figure 4.4 Setup for Optical dosimetry in a liquid phantom. The optical dosimetry probe is translated within a plexiglas cuvette filled with liquid phantom, and illuminated by an NIR source.

In order to quantify the photon fluence ($\Phi_{\text{joules}}$) in J/cm$^2$, we converted the output of the Monte Carlo fluence ($\Phi$, photons/mm$^2$) as follows:

$$\Phi_{\text{joules}} = \Phi \frac{hc}{\lambda} \quad (4.6)$$

where h is Planck’s constant (6.626e-34 J.s), c and $\lambda$ are the speed and wavelength of light in the medium. The energy deposited in the tissue is obtained by multiplying the photon fluence with the absorption coefficient $\mu_a$ and the volume of the voxel (v):

$$\Phi_{\text{absorbed}} = \Phi \frac{hc}{\lambda} \mu_a v \quad (4.7)$$
4.3 Results

4.3.1 Optical Dosimetry and Monte Carlo Validation in Homogeneous Phantoms

The optical fluence measured by the dosimetry probe in white and gray matter phantoms was compared to the Monte Carlo generated fluence. The design of optical phantoms is crucial for accurately determining the localized distribution of fluence with the probe before validating it using Monte Carlo. Figures 4.5 and 4.6 show the comparison between the probe measurements and the Monte Carlo in brain phantoms for two different illumination profiles, the flat diffuse beam produced by the integrating sphere and the super-Gaussian beam emanating from the optical fiberguide. Comparisons were made along the central axis of the beam and in the direction perpendicular to the beam axis at different depths, as shown in figure 4.7. These plots reveal the energy fluence measured by the probe matched Monte Carlo simulations both along and perpendicular to the beam direction.
Figure 4.5 Optical dosimetry in white and gray matter phantoms. The photon source used is an integrating sphere connected to a pulsating laser source. The graphs show the exponential decrease of photon fluence along the beam axis in white and gray matter mimicking phantoms. The Monte Carlo generated fluence closely matches the fluence measured by the probe.
Figure 4.6 Optical dosimetry in white matter, gray matter and skull bone phantoms. The photon source used is an optical fiberguide (connected to a pulsating laser source) with a super-Gaussian beam distribution. The Monte Carlo generated fluence closely matches the fluence measured by the probe. This shows that the Monte Carlo beam modeling can be reliably used as a reliable estimator of photon energy distribution in tissue phantoms.
Figure 4.7 Lateral beam profile measurement using optical dosimetry probe and validation by Monte Carlo in homogeneous phantoms. (A) Beam profile in air using calorimeter. Optical dosimetry measurements validated MC simulated lateral beam profiles in phantoms of: (B) white matter, (C) gray matter and (D) skull bone, i.e., perpendicular to the beam axis. The measurements were normalized along the illumination axis. Cuvette dimensions: 5.3cm x 4.6cm x 3.1cm, thickness = 0.4cm.
Figure 4.8 Continued
The average relative % error of the Monte Carlo relative to the probe measurements is 11.27% for white matter, 13.25% for gray matter and 11.81% for skull bone along the beam axis for a range of 0.2-2cm within the phantom, while perpendicular to the beam axis, the % relative error is 9.4%, 12.06%, and 8.91% for white matter, gray matter and skull bone phantoms. These systematic errors represent the levels of confidence with which the Monte Carlo matches the probe measurements, see tables 4.3 and 4.4.

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Error% (0.2-1 cm)</th>
<th>Error% (1-2 cm)</th>
<th>Average error%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter</td>
<td>12.13</td>
<td>10.5</td>
<td>11.27</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>13.39</td>
<td>30.12</td>
<td>13.25</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>11.39</td>
<td>12.28</td>
<td>11.81</td>
</tr>
</tbody>
</table>
Table 4.4 % Mismatch Error in Homogeneous Phantom perpendicular to beam axis (z)

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Error% z=0.2cm</th>
<th>Error% z=0.6cm</th>
<th>Error% z=1.0cm</th>
<th>Error% z=1.4cm</th>
<th>Average error%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter</td>
<td>10.34</td>
<td>13.34</td>
<td>9.14</td>
<td>4.79</td>
<td>9.4</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>13.45</td>
<td>11.52</td>
<td>14.29</td>
<td>8.97</td>
<td>12.06</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>8.41</td>
<td>5.69</td>
<td>12.64</td>
<td></td>
<td>8.91</td>
</tr>
</tbody>
</table>

An analysis of the fluence profile within the skull phantom showed that the super-Gaussian beam fluence decreases with an effective attenuation coefficient of 4.818 cm\(^{-1}\). This factor was used to estimate the effectiveness of therapy for different skull thicknesses. Based on the validated Monte Carlo method, the power transmitted by the fiberguide source for various skull thicknesses are 5.9 mW/cm\(^2\) (0.4 cm thick), 2.16 mW/cm\(^2\) (0.6 cm thick), 0.83 mW/cm\(^2\) (0.8 cm thick), 0.33 mW/cm\(^2\) (1 cm thick). Thus, the % power transmitted in a 1 cm thick adult skull is 1.8%, while a pediatric skull of 0.4 cm thickness would allow 33.5% optical power to reach the soft tissue. The thickness
of the skull and its density determines the overall attenuation and hence optical planning protocols which can be obtain from a CT scan (see chapter 6).

4.3.2 Optical Dosimetry and Monte Carlo Validation in Heterogeneous Brain Phantoms

Fluence profiles measured in the white matter solution in the layered heterogeneous phantom (1.1 cm skull agar phantom, 1.1 cm gray matter agar phantom, 5.9 cm white matter liquid phantom in the said order), showed a good degree of match between the Monte Carlo simulated data and the probe measurements, see figure 4.8. The exponential decrease in fluence along the beam axis is shown on the right side of figure 4.8 while the lateral beam profiles at different depths above the gray matter agar surface is shown on the left side of this figure. The lateral fluence profiles have been normalized to the intensity at a depth of 0.2cm above the gray matter agar surface, while the fluence profiles along the beam axis were normalized to the fluence at z = 0.1cm above the gray matter agar surface. The average systematic error (relative % error) between the probe and Monte Carlo fluences is 17.71% along beam axis and 18.04% perpendicular to the beam axis and is shown in tables 4.5 and 4.6. The validation of optical dosimetry results in the complex layered phantom validate that the beam spread can be estimated correctly by the Monte Carlo if the optical coefficients of the phantom are known.
Figure 4.9 Validation of Monte Carlo in a heterogeneous phantom (1.1cm skull agar, 1.1cm gray matter agar and 5.9cm white matter liquid). Lateral profile measurements (in the white matter phantom solution) are shown on the left while axial comparison is on the right. The depth shown by z is the distance from the gray matter agar surface. Cuvette dimensions: 9.4cm x 9.4cm x 10.9cm, thickness = 0.3cm.

Table 4.5 % Mismatch Error in Heterogeneous Phantom along beam axis (z)

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Error%</th>
<th>Error%</th>
<th>Average error%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.1-1 cm)</td>
<td>(1-2 cm)</td>
<td></td>
</tr>
<tr>
<td>White Matter (over Skull and Gray Matter layers)</td>
<td>2.11</td>
<td>33.32</td>
<td>17.71</td>
</tr>
</tbody>
</table>

Table 4.6 % Mismatch Error in Heterogeneous Phantom perpendicular to beam axis (z)

<table>
<thead>
<tr>
<th>Phantom</th>
<th>Error% z=0.2cm</th>
<th>Error% z=0.4cm</th>
<th>Error% z=0.6cm</th>
<th>Error% z=1cm</th>
<th>Average error%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter (over Skull and Gray Matter layers)</td>
<td>18.52</td>
<td>15.09</td>
<td>15.37</td>
<td>23.17</td>
<td>18.04</td>
</tr>
</tbody>
</table>
4.4 Discussion

We validated the 3D Monte Carlo code using the TiO₂ based dosimetry probe measurements in phantoms resembling white matter, gray matter and skull bone. When comparing absolute fluence measurements, the error between MC simulated data and measured data was less than 25 percent within these homogeneous tissues. The independent characterization of the probes and the optical phantoms using calorimeter gold standard and spectrophotometer demonstrated the validity of using the probe as a gold standard. Studies were performed for two different types of NIR light sources in different optical phantoms, and the ease of photon quantification to absolute dose (in mW/mm² or J/mm²) proves the fidelity of the Monte Carlo as a predictive tool to accurately estimate 3D photon energy distribution in complex media. The measurement and prediction accuracy can be improved with better instrumentation for probe localization and better laser beam positioning setups. The boundary conditions of the phantom play a very important role in the Monte Carlo results and need to be simulated accurately. This includes the accurate depiction of cuvette/phantom dimensions, distance from the source and source dimensions.

This study achieves the first step of designing the tools necessary to validate the NIR photon distribution in three dimensions in optical phantoms. By quantifying the energy fluence and local deposited dose will allow an accurate depiction of the rate and quantity of drug release. Critical to these simulations is the accurate determination of the tissue structure and boundaries, which can be determined using imaging modalities
such as MRI or CT scan to segment various tissue types and obtain an optical property map. This can now be seamlessly input into the Monte Carlo under various illumination conditions.
5 SPECIFIC AIM3: EMPIRICAL APPROACH TO PHOTON PROPAGATION

5.1 Introduction

Translating an optical planning tool into the clinic requires simulations to be performed in time frames that are feasible. Monte Carlo simulations takes a few hours of execution time to generate statistically significant number of photons for full brain, and this is for a single laser source. Obtaining an optimal optical treatment plan requires dose calculations for multiple laser sources and iterations to ensure maximal light delivery to the target tissues. Hence, even though the CUDA based platform enhances the speed of the Monte Carlo by 300X over CPU based models [61], it still would need to be significantly accelerated to be provide treatment plans in a clinical setting. This can be accomplished by purchasing a cluster of NVIDIA cards (costly). Instead, this motivated us to design an empirical model approach to estimate photon propagation in complex heterogeneous tissues, which could have a runtime of less than a minute while providing a reasonable level of accuracy [64].

A number of analytical solutions are made to the radiative transport equation, also known as the Boltzmann transport equation [82]:

\[ \Omega \cdot \nabla \psi(r, \Omega) + (\mu_a(r) + \mu_s(r))\psi(r, \Omega) = S(r, \Omega) + \mu_s(r) \int_{4\pi} \psi(r, \Omega') p(\Omega, \Omega') d\Omega' \]  (5.1)
In the above equation, $S(r, \Omega)$ is source term and describes the power injected into a solid angle defined by $\Omega$ within a unit volume at position $r$; $\Omega$ is the photon propagation unit vector; $\psi(r, \Omega)$ is the radiance energy (units: W.cm$^{-2}$.sr$^{-1}$); $r$ is position vector; $p(\Omega, \Omega')$ is the phase function and represents the probability of photon scattered from direction $\Omega'$ to $\Omega$.

The fluence, $\Phi(r)$, is obtained by summing the energy radiance, $\psi(r, \Omega)$, over all directions [82]:

$$
\Phi(r) = \int_{4\pi} \psi(r, \Omega) d\Omega. \quad (5.2)
$$

Solving the radiative transport equation can be solved using finite difference methods under certain approximations [82]. One such method is the DANTSYS (diffusion accelerated neutral particle transport code system) [82].

The diffusion approximation (P1 approximation) is the most commonly used analytical approximation to the radiation and is used widely to calculate fluence in homogeneous and heterogeneous tissues and is given by the equation [82, 83]:

$$
\frac{1}{c} \frac{\partial \Phi(r,t)}{\partial t} + \mu_a \Phi(r,t) - \nabla [D \nabla \Phi(r,t)] = S(r,t). \quad (5.3)
$$

The diffusion equation can thus be used to derive the optical fluence in homogeneous and heterogeneous tissues by using diffusion synthetic acceleration method (DANTSYS)
and employs a corrected diffusion equation to accelerate the convergence of transport iterations. The use of the diffusion equation results in under-estimation of fluence in media with a high ratio of absorption to scattering coefficients [82, 84]. The Monte Carlo method thus remains the only method to accurately simulate photon fluence over a wide range of albedos.

In our study, we investigated a voxel-based, nearest neighbor weight based method trained using Monte Carlo simulated data. In retrospect, this approach is similar to the photon convolution method [85], but uses arbitrary weights to determine photon scatter at each location (voxel) in a 3D volume. The absorption of photons in each voxel is determined using the Beer Lambert’s law [78] and the optical absorption coefficient. The photon dose distribution is simulated in a 3D voxelated format for easy comparison and 3D optimization with the Monte Carlo and allows seamless integration with medical imaging modalities such CT and MR, used to characterize tissue heterogeneity and object boundaries of the medium. The empirical nature of this software can be easily adapted to different optical properties and voxel sizes by adjusting the scattering weights, while the absorption coefficient remains unchanged. As with the MC code, different beam profiles and upstream optics can be seamlessly integrated to improve its applicability. Realization into CUDA can provide corrective algorithms on the order of a few seconds and real-time applications.
5.2 Materials and Methods

5.2.1 Algorithm Design

The Empirical approach is based on the assumption that the photon fluence in a voxel in a particular layer is a weighted sum of the fluences of neighboring voxels in the previous layer [63, 64]. The basic concept and schematic of this algorithm is illustrated in figures 5.1-5.3. The steps of the algorithm can be summarized as follows:

1. Assign the incident photon beam distribution (e.g. super-Gaussian beam) to the first layer of voxels. In this case, we assume that the direction of photon propagation is in the +z direction.

2. For every voxel in a layer, calculate the directional scatter components. The equation 8 represents an example of how the forward scatter component is calculated. The coordinates i, j, k denote the x, y and z location of the voxel. The arbitrary weights wt1 and wt2 are forward and diagonal weights, which determine the percentage of scatter. The sum of all weights is always equal to one (i.e. wt1+4*wt2=1), so that the total fluence entering a voxel is equal to the sum of fluence absorbed and exiting the voxel. The equations used to calculate the other components can be similarly determined. The sum of all the scatter components in a voxel equals the total fluence in that voxel (arbitrary units: photons/unit volume).

3. Calculate absorbed energy (I_{abs}) using Beer Lambert’s law for a path length dl = voxel length, based on the absorption coefficient (\mu_a) of the voxel:

\[ I_{abs}(i, j, k) = I(i, j, k)(1 - e^{-\mu_a dl}) \] (5.4)
4. Calculate and accumulate the fluence over all voxels in the current layer and increment z to proceed to the next layer. Continue propagation till the fluence exits the volume.

An example of the implementation of this algorithm in 3D matrices using nested “for loops” is shown in figure 5.3 (A). The purpose of this flowchart is to explain the details of the algorithm from the perspective of its implementation. Different iterating loops and several different data structures are possible to implement this algorithm based on the memory and performance requirements.

We implemented an iterative routine, shown in figure 5.3 (B), in order to ensure that residual fluences exit the 3D volume. The rationale behind this step is that some side-scatter and back-scatter components are significantly high in media with high scattering coefficients (e.g. white matter). While the software is implemented in the form of a primarily forward propagation direction, it leaves behind residual fluence components which do not contribute to the total fluence and which do not exit the volume. Thus in order to ensure that all residual photons leave the volume, we implemented an iterative routine to propagate photons in the forward (+z) and reverse (-z) directions alternatively. This was implemented in an iterative fashion. In the first iteration we propagate the photons in the +z direction while in the next iteration the matrices are flipped (along the x, y, z planes) such that +z direction now refers to the −z, +x refers to the −y and +x refers to the −x directions. In other words the matrix is turned upside down. The
empirical code is run again (without any additional input fluence) such that the iteration
is mainly in a direction opposite to the first iteration. We again flip the matrix to its
original orientation before running the empirical iteration. This is continued until we
ensure that most photons have exited the volume and the residual fluences are below a
certain threshold. In our study we found that 14 iterations were sufficient to ensure that
most photons have exited the volume. It is important to note that the iterative routine
mainly ensures a better match with Monte Carlo in the lateral direction (in xy plane)
away from the beam axis. The number of iterations has less effect on effective
attenuation at the center of the beam where most of the fluence is contributed to by
the forward directional fluence vector.

Figure 5.1 The Empirical photon propagation [64]: The photons in a voxel is propagated
to neighboring voxels using scatter weights.
Figure 5.2 Integral or accumulation of fluence in a voxel. [64]. The directional fluences such as forward (If), diagonal upwards (Id), diagonal downwards (Idb) and side (Is), entering a voxel are weighted and summed using forward (wt1) and diagonal weights (wt2). Fluence is redistribution conserved by ensuring that (wt1 + 4 x wt2) = 1.
Figure 5.3 A) Implementation of the 3D Empirical algorithm using nested loops. Photons are propagated in the simulation by iterating over a 3D matrix. The matrix dimensions in the x, y, z coordinates are dim1, dim2 and dim3 respectively, while (i, j, k) are (x, y, z) coordinates of a voxel in the volume. B) Iterative routine to run the Empirical algorithm.

In each iteration we check if the sum of the residual fluences are below a certain threshold. If the residual fluences are still high, we run the empirical code iteratively to ensure that the residual fluences have exited the volume. In our study we use 14 iterations for the neonatal head simulations, while 1 iteration is sufficient for homogeneous phantoms. The iterative routine is seen to be more effective for highly scattering tissues with a significant amount of back-scatter.
5.2.2 Optimization of the Empirical Algorithm using Monte Carlo

The GPU based Monte Carlo was used to derive the weights, which depended upon the reduced scattering coefficient of the medium. The weights were obtained by an iterative optimization procedure that compared the output fluence of the empirical algorithm to that generated by the Monte Carlo the fluence along the central beam axis. The weights which show the best possible match defined by the highest R-square coefficient are selected to calibrate the empirical method. Tables 5.1 and 5.2 show the weights \( wt_1 \) and \( wt_2 \) obtained for different tissue types and voxel sizes. The absorption coefficient is
scaled to the voxel size and the photons are absorbed before proceeding to the next layer.

5.3 Results

5.3.1 Empirical Optimization results

In this section we describe the optimization studies performed on the Empirical algorithm. Both these studies were performed separately for brain tissues and tissue phantoms, mainly due to the difference in their optical anisotropy factors, which leads to subtle changes in fluence distributions. Table 5.1 shows the weights derived for brain tissue phantoms (composed of India ink and Intralipid), while table 5.2 shows the weights for real brain tissues. The optical properties of brain tissues are shown in table 4.1 while those of the tissue phantoms are shown in table 4.2. The corresponding comparison in fluence profiles along the beam axis is shown by figure 5.4 for brain tissue phantoms and by figure 5.5 for real brain tissues. The difference in the properties mainly arises from the difference in the anisotropy factor between intralipid and the brain tissues. Thus while we have achieved a match in the reduced scattering coefficient between the phantoms and the real tissues, the photon distribution varies to some extent between tissues and phantoms, as seen by Monte Carlo simulations. Hence we trained the Empirical algorithm to match the match the Monte Carlo generated fluence separately for both brain tissues and tissue phantoms. The different resultant weights derived between phantoms and tissues also validates the purpose.
We also did a comparison of lateral fluence profiles generated by the Monte Carlo and the Empirical and these are shown in figures 5.6 - 5.9. While the optimization routine used the match in fluence attenuation along the beam axis as the main criteria, we tried to see if this translates into a match along the lateral direction at different depths (z=2mm, z=5mm, z=10mm, z=15mm) in homogeneous tissues. Our analysis shows that the lateral profiles of the Empirical algorithm closely match those of the Monte Carlo under similar illumination and boundary conditions.

<table>
<thead>
<tr>
<th>Tissue Phantom</th>
<th>Voxel Size (mm)</th>
<th>Wt1</th>
<th>Wt2</th>
<th>R-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter</td>
<td>0.1</td>
<td>0.949461</td>
<td>0.012635</td>
<td>0.99999</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>0.1</td>
<td>0.87469</td>
<td>0.031328</td>
<td>0.999969</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>0.1</td>
<td>0.914828</td>
<td>0.021293</td>
<td>0.99979</td>
</tr>
<tr>
<td>White Matter</td>
<td>1</td>
<td>0.474876</td>
<td>0.131281</td>
<td>0.99992</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>1</td>
<td>0.062097</td>
<td>0.234476</td>
<td>0.999828</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>1</td>
<td>0.245949</td>
<td>0.188513</td>
<td>0.999871</td>
</tr>
</tbody>
</table>
Figure 5.5 Optimization phase for Brain Tissue Phantoms. The optical properties of phantom materials (India ink and Intralipid) from table 4.2, are used by the MC. A flat broad beam (2cm diameter) is simulated using Monte Carlo and the Empirical algorithm is optimized to match the Monte Carlo with the identical illumination conditions [63].

<table>
<thead>
<tr>
<th>Tissue Phantom</th>
<th>Voxel Size (mm)</th>
<th>Wt1</th>
<th>Wt2</th>
<th>R-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter</td>
<td>0.1</td>
<td>0.931723</td>
<td>0.017069</td>
<td>0.999985</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>0.1</td>
<td>0.904809</td>
<td>0.023798</td>
<td>0.999976</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>0.1</td>
<td>0.931898</td>
<td>0.017025</td>
<td>0.999985</td>
</tr>
<tr>
<td>Tumor (Astrocytoma)</td>
<td>0.1</td>
<td>0.954234</td>
<td>0.011442</td>
<td>0.999991</td>
</tr>
<tr>
<td>White Matter</td>
<td>1</td>
<td>0.292641</td>
<td>0.17684</td>
<td>0.999898</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>1</td>
<td>0.115763</td>
<td>0.221059</td>
<td>0.99984</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>1</td>
<td>0.306998</td>
<td>0.173251</td>
<td>0.999885</td>
</tr>
<tr>
<td>Tumor (Astrocytoma)</td>
<td>1</td>
<td>0.51633</td>
<td>0.120917</td>
<td>0.999896</td>
</tr>
</tbody>
</table>
Figure 5.6 Optimization phase for Brain Tissues. The brain tissue properties from table 4.1 are used by the Monte Carlo. A flat broad beam (2 cm diameter) is simulated using Monte Carlo and the Empirical algorithm is optimized to match the Monte Carlo with the identical illumination conditions.
Figure 5.7 Lateral Beam profile comparison between Empirical and Monte Carlo for Gray Matter tissue. A flat broad beam (2cm diameter) is simulated.
Figure 5.8 Lateral Beam profile comparison between Empirical and Monte Carlo for White Matter tissue. A flat broad beam (2cm diameter) is simulated.
Figure 5.9 Lateral Beam profile comparison between Empirical and Monte Carlo for Skull Bone tissue. A flat broad beam (2cm diameter) is simulated.
5.3.2 Empirical Validation using Dosimetry Probe

The Empirical algorithm was compared to Monte Carlo simulate data and probe measurements in homogeneous phantoms with known optical properties to validate the Empirical code for super-Gaussian beam profile.
Figure 5.10 shows the comparison between the Monte Carlo, Empirical and Probe measurements in brain tissues for broad beam simulations in homogeneous phantoms. The weights derived for tissue phantoms are different from tissues. For the tissue phantoms, the weights used are from table 5.1. The beam simulated in a super-Gaussian beam as described in chapter 4. The super-Gaussian beam can be easily simulated using the Empirical as it allows us to set the photon distribution at any voxel. The average relative % error between the Empirical and Probe measurements is 10.2% for White Matter, 45.2% for Gray Matter and 22.1% for Skull Bone phantoms; while the comparison between Empirical and MC is 22.6% for White Matter, 35.8% for Gray Matter and 21.9% for Skull Bone phantoms. The probe measurements validate the Empirical results and the Monte Carlo in homogeneous phantoms.
Figure 5.11 Comparison of the Empirical algorithm with Monte Carlo and Probe measured fluence in brain phantoms resembling white matter, gray matter and skull bone. The illumination source used is a super-Gaussian beam, which is emulated by the Monte Carlo and the Empirical algorithm. The empirical approach is a close approximation of the Monte Carlo and the probe over the range of optical properties of brain tissues. [63].

5.3.3 Simulations in Head Phantoms

We simulated head phantoms to compare the Monte Carlo and Empirical fluence and energy distributions. The phantom simulated had the dimensions of a child’s head. The simulation studies were done in the presence (figures 5.11 - 5.14) and absence (figures 5.15 – 5.18) of tumor to study how well the Empirical photon distribution matches the Monte Carlo. 2D photon energy maps were also generated and compared. The weights used for the simulations were those of real brain tissues as shown in table 5.2. While the
Monte Carlo only generates the fluence map, the energy map is derived from the fluence map by multiplying the fluence with the absorption coefficient and the volume of the voxel.

In the case of the normal head phantom (without tumor) of 100mm diameter, the boundary conditions and tissue dimensions are shown in figure 5.11. The skull thickness is 4mm; thickness of gray matter is 10mm, while the center of the head is mainly white matter with a diameter of 72mm. The phantom is illuminated with a 20mm diameter uniform beam (800nm wavelength). Figure 5.12 shows the comparison plot of the energy deposition between the Monte Carlo and the Empirical along the beam axis. The first point on the plot starts at the point where the light enters the skull tissue (i.e. depth=0 in the plot of figure 5.12 corresponds to z=6 along the beam axis in figure 5.11). Similarly, figure 5.13 shows the log normalized fluence plot along the beam axis. Both the fluence and the energy plots show that the Empirical fluence and energy simulated closely follow those of the Monte Carlo within a certain error. The energy distribution maps in 2D are shown in figure 5.14. Note that the Monte Carlo generated map suffers from extremely low photon fluence at depths larger than 5cm due to low photon statistics (restrained by the time for head simulations), while the Empirical algorithm does not suffer from this limitation.

We also studied the performance of the Empirical algorithm in a head phantom in the presence of a tumor (astrocytoma) of 5mm diameter. The boundary conditions of other
tissues are similar to those of the normal head phantom in the previous case and are shown in figure 5.15. The tumor presence significantly changes the fluence and energy distributions as shown in figure 5.16 and figure 5.17 respectively, compared to the normal head. The fluence perturbation is mainly at the site of the astrocytoma which shows higher energy absorption as shown in figure 5.16. The difference between the fluences generated by the Empirical and the Monte Carlo has a certain difference, which also translates into an error in the energy distributions. However as seen in the plots, this error is constant and can be easily quantified. The photon energy maps are shown in figure 5.18.

![Figure 5.12 Simulation of a head phantom for comparing the Empirical and Monte Carlo models in heterogeneous brain tissues.](image)
Figure 5.13 Comparison of photon energy distribution between the Empirical algorithm and Monte Carlo in a head phantom, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.11).
Figure 5.14 Comparison of photon fluence distribution between the Empirical algorithm and Monte Carlo in a head phantom, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.11).
Figure 5.15 Comparison of photon energy distribution images (2D) between the Empirical algorithm and Monte Carlo in a normal head phantom.
Figure 5.16 Simulation of a head phantom with tumor (astrocytoma) for comparing the Empirical and Monte Carlo models in heterogeneous brain tissues.

Figure 5.17 Comparison of photon energy distribution between the Empirical algorithm and Monte Carlo in a head phantom with tumor, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.15).
Figure 5.18 Comparison of photon fluence distribution between the Empirical algorithm and Monte Carlo in a head phantom with tumor, along the beam axis. The illumination source used is a uniform beam of 2cm diameter. The plot is from the point where light enters the skull bone (refer to figure 5.15).
Figure 5.19 Comparison of photon energy distribution images (2D) between the Empirical algorithm and Monte Carlo in a head phantom with tumor (astrocytoma).
5.3.4 Simulating Fluence Buildup

The effect of fluence buildup is seen in Monte Carlo simulations near the photon source. This effect largely depends on the albedo of the optical medium, where larger albedos enhances this buildup effect compared to smaller values and is significant within 1mm from the source in brain tissues. While the Empirical can closely match the Monte Carlo over diffusion region, the existing derived weights were inadequate to simulate the fluence build up; therefore, a new set of weights were derived. Plots for the best possible match in white matter, gray matter, skull bone, and astrocytoma are shown in figures 5.19-5.22, respectively, and their corresponding weights are listed in table 5.3. While the Empirical model may not exactly match Monte Carlo simulated data for both the diffuse and near-source regions at the same time, it can modified to match the MC based on the region of interest. One must note that the problem of fluence build occurs within the first millimeter or two, thus a smaller voxel size will be required.
Figure 5.20 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for White Matter.

Figure 5.21 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for Gray Matter.
Figure 5.22 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for Skull Bone.

Figure 5.23 Comparison of the buildup fluence buildup between Monte Carlo and Empirical Model for Tumor (Astrocytoma).
Table 5.3 Weights derived to obtain fluence buildup

<table>
<thead>
<tr>
<th>Tissue Phantom</th>
<th>Voxel Size (mm)</th>
<th>Wt1</th>
<th>Wt2</th>
<th>R-square</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Matter</td>
<td>0.1</td>
<td>0.637486</td>
<td>0.090629</td>
<td>0.995372</td>
</tr>
<tr>
<td>Gray Matter</td>
<td>0.1</td>
<td>0.711962</td>
<td>0.07201</td>
<td>0.999807</td>
</tr>
<tr>
<td>Skull Bone</td>
<td>0.1</td>
<td>0.735052</td>
<td>0.066237</td>
<td>0.994337</td>
</tr>
<tr>
<td>Tumor (Astrocytoma)</td>
<td>0.1</td>
<td>0.89585</td>
<td>0.026037</td>
<td>0.955473</td>
</tr>
</tbody>
</table>

5.4 Discussion

In this specific aim, a reasonable accuracy (R-square of 0.999) was achieved between the Empirical and the Monte Carlo for homogeneous and heterogeneous brain phantoms and validated using the optical dosimetry probe. Overall, the empirical model provides an alternate voxel based approach of estimating photon fluence in 3D heterogeneous tissues besides the diffusion approximation and Monte Carlo methods. Even though it was less accurate compared to Monte Carlo simulated data, (up to 36% error between probe and empirical), the reduction in computation times (8 hours per MC simulation versus 4-12 seconds of Empirical simulation), provides a means for clinical and preclinical applications, in particular for large data sets and iterative-based optimization routines. Similar to the GPU MC code, it is easily integrated with existing imaging modalities such as CT and MR due to its voxelated structure. In order to simulate fine structural boundaries of brain tissues, we need a fine resolution of around 1mm, for which the CT dataset becomes very large. For such large datasets, where the Monte Carlo cannot be run iteratively (>24 hours execution time), the empirical
algorithm can replace the Monte Carlo for preliminary analysis. More study is required to investigate the % match due to difference in the optimization routine and the dependence of weights on the scattering properties of the medium. Further research is also needed to understand the mismatch at object boundaries, particularly at larger depths.
6 SPECIFIC AIM4: IMAGE-GUIDED OPTICAL TRANSMISSION STUDIES IN HUMAN SKULL BONES

6.1 Introduction

The skull forms an optical attenuator (absorber and scatterer) in the transmission of near-Infra-red light to the brain. The success of any NIR based imaging or therapeutic technique involving the brain depends on an accurate and precise determination of the optical transmission properties of the skull. The skull bone consists of osteocytes and calcium deposits in various densities and complex geometries based on different anatomical locations in the skull. Previous studies have looked at the optical transmission properties of different tissues [93-99] using collimated laser beams with powers ranging from 10mW/cm² to 25mW/cm² [93, 94]. These studies included NIR transmission through human cadaver skulls [94]. In our study, we used an NIR laser source (17.64mW/cm²) with a complex super-Gaussian broad beam profile and investigated if a relationship between voxel-based HU and optical attenuation exists. Simulated Monte Carlo data was compared to measured beam intensity and distribution implementing the TiO₂-based optical dosimetry probe. This data was used to investigate the relationship between the HU from CT images and the optical attenuation by measuring the transmitted NIR light through human cadaver skulls. Critical to these measurements is the ability to quantify low power fluence transmitted through the skull.
afforded with the TiO2 optical dosimetry probe compared to the calorimeter used in previous bone transmission studies [91, 92].

To date, studies [80, 100-102] have measured the optical properties of the brain tissues, have mapped the heterogeneity and inter-sample variations. The comparison of the optical properties of skull bone found in these studies [80, 100-102] is shown in table 6.1. It shows a wide variation in the optical properties reported for the human skull bone. A comprehensive work by Bashkatov et al. [100] mapped these variations in optical properties of the skull bone at different wavelengths. Our aim is to further understand this complexity caused by variations in the bone density and bone thickness to map out an accurate fluence map of the Monte Carlo in the brain. The use of Computed Tomography images provides a 3D map of the heterogeneous bone structure and allows us to accurately generate the boundary conditions and density maps using the Monte Carlo.

<table>
<thead>
<tr>
<th>Study By</th>
<th>Absorption Coefficient ($\mu_a$) (cm$^{-1}$)</th>
<th>Scattering Coefficient ($\mu_s$) (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firbank et al.</td>
<td>0.24</td>
<td>18.4</td>
</tr>
<tr>
<td>Bashkatov et al.</td>
<td>0.11</td>
<td>19.48</td>
</tr>
<tr>
<td>Pifferi et al.</td>
<td>0.07</td>
<td>12.5</td>
</tr>
<tr>
<td>Ugryumova et al.</td>
<td>0.25</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 6.1 Optical properties of skull bone measured at 800nm wavelength in different studies [80, 100-102]. The anisotropy factor ($g$) is 0.9.
6.2  Materials and Methods

6.2.1  Optical Bone Dosimetry Setup

10 Different skull bone samples [courtesy: Lisa Hilliard (Medical Laboratory Science Program) and Dr. James Walker (Dept. of Basic Medical Sciences)] were used for the optical transmission study. The light source consisted of the optical fiberguide (see chapter 2) connected to a laser source. The NIR output of the fiberguide was measured using a calorimeter to be 19.94mW or (17.64 mW/cm²) at 800nm wavelength. For transmission studies, the optical fiberguide was placed against the outer surface of the skull bone, such that its aperture was flat against the bone surface, thus providing a normal exposure. The fluence transmitted through the bone was measured using the TiO₂ dosimetry probe by placing it against the inner surface of the skull bone, opposite the fiberguide on the other side of the skull, which was ensured by locating the point of maximum fluence. The energy fluence for 5 points or locations per skull was acquired, and at each location the measurement was repeated three times. A total of 10 cadaver skull bones were measured, which gave a total of 50 measurement data points. The setup for these experiments is shown in figures 6.1 and 6.2.
Figure 6.1 Setup to measure the optical transmission of NIR light through the skull bone. The source used is an optical fiberguide connected to a laser. The NIR fluence collected by the probe tip is carried by an optical fiber to a PIN photodiode circuit, whose electrical output is read using an oscilloscope (right).

For the lateral beam profile measurements, each skull was placed in a large Plexiglas cuvette such that the point of illumination (marked previously on the skull surface) was directly in contact with the cuvette bottom. The transparent optical bench helped in alignment of the skull and the source with good precision. The experimental setup is shown in figures 6.2 and 6.3. The lateral profile was first measured in air and in water 0.5cm from the inner skull surface. While measurement in air was for further validation of optical transmission, the measurement in water was for a more realistic scenario, where the refractive index of water is similar to that of water.
Figure 6.2 Skull bone sample (top portion) used in the experiment. The dosimetry probe is also seen.

Figure 6.3 Optical dosimetry setup for lateral beam profile measurement in skull sample.
6.2.2 Acquisition and Processing of CT Images of the Skull Bone

Computed Tomography (CT) was used to map optical boundaries and density of the bone on a Philips Brilliance CT scanner. The CT images were acquired at 300 mAs and 120 kVp, and reconstructed with a slice thickness of 0.67mm, pixel size (xy plane) of 0.2344mm, and the bone kernel. The points for measurement on each skull phantom were labeled using CT contrast beads and marked with a pencil (see Figure 6.5), which were used to identify the points of illumination.

Figure 6.5 shows the use of CT contrast beads to mark the point of illumination on the skull samples. The CT images were displayed and processed using Matlab based software, which was custom developed to identify the source and detector positions and simulate the bone boundaries on CT images, as shown in figure 6.5. The point of
measurement for optical transmission lies on the inner skull boundary on the line while lateral profile is measured at 0.5 cm from the inner skull surface.

In order to identify the source voxel for illumination, another line was drawn tangential to the skull surface, passing through the intersection point of the bead and the outer skull surface as shown in figure 6.5 (B). The cross product of the illumination vector and the source tangential vector is the other vector which also lies tangential to the skull surface along the z axis [0 0 1]. The source voxels are then identified as those lying on the 3D circle defined by the two tangential vectors. The parametric equation used of a 3D circular disk [103] can be then used to represent the fiberguide source surface as described by the two tangential vectors. Thus one can accurately represent any broad source in the Monte Carlo at any arbitrary angle as used in the experimental setup.
Figure 6.5 The CT image of a skull bone is processed in Matlab to extract the source directional vector (A) and in-plane source vector (B) by drawing lines (blue) on the image and extracting the end points of the lines to calculate the vectors. The third vector is the cross product of these two vectors and is in the plane of the source.

6.3 Results

6.3.1 Optical Transmission Measurements in the Skull

The result for the optical transmission for 10 different phantoms is shown in figures 6.6, 6.7 and 6.8. Note that the phantoms are numbered from 1-4 and 6-11 as phantom 5 was
not used (incomplete CT scan). The optical transmission measurements show a wide variation in the optical power transmitted, due to variation in skull thickness and (heterogeneity in) bone densities. In order to map the Monte Carlo fluence to the % transmission measurements of the probe, we used CT images to determine the optical path-length through the bone (i.e. skull thickness in the direction of illumination). The skull thicknesses measured using CT images showed different skull thicknesses both within and across the skull samples. The measured skull thicknesses from the CT images are shown in figure 6.9. We also measured the lateral beam profiles in the skull phantoms in air and water as shown in figure 6.10. The measured probe voltage is seen to be higher in water compared to air. This is mainly due to the difference in the skull-medium interface boundary conditions, such as the differences in the refractive indices of skull bone and water versus skull bone and air.
Figure 6.6 Percentage fluence transmitted for phantoms 1-4 measured using the probe calorimeter setup.
Figure 6.7 Percentage fluence transmitted for phantoms 6-9 measured using the probe calorimeter setup.
Figure 6.8 Percentage fluence transmitted for phantoms 10-11 measured using the probe calorimeter setup.

Figure 6.9 Skull thicknesses measured across skull samples using CT image data. Measurement points: Phantom1 (1-5), Phantom2 (6-10), Phantom3 (11-15), Phantom4 (16-20), Phantom5 (21-25), Phantom6 (26-30), Phantom7 (31-35), Phantom8 (36-40), Phantom9 (41-45), Phantom10 (45-50).
Figure 6.10 Lateral beam profile (fraction transmitted) measured using the dosimetry probe in air and water 0.5mm from the inner skull surface.

6.3.2 Comparison with the Monte Carlo

Based on the three different sets of optical properties of the skull bone shown in table 6.1, three Monte Carlo profiles were obtained with a super-Gaussian beam distribution. The fluence profiles along and perpendicular (lateral profile) are shown in figures 6.11 and 6.12 respectively. The Monte Carlo simulations show that different optical properties of the skull bone will give rise to different transmission characteristics, which could result in different transmission factors and lateral beam profiles. The lateral beam profiles due to different optical properties also show the variations between the three models.
Figure 6.11 MC simulated fluence profiles along beam axis for a homogeneous skull medium generated using Monte Carlo simulations for three sets optical properties of the skull bone (Ugrynova et al, Pifferi et al, Firbank et al, and Bashkatov et al). A broad beam super-Gaussian NIR source (800nm wavelength) was simulated.
Figure 6.12 MC simulated lateral fluence profiles at different depths (z=0,2,4,6mm) for a homogeneous skull medium generated using Monte Carlo simulations for three sets of optical properties of the skull bone (Ugrynova et al, Pifferi et al, Firbank et al, and Bashkatov et al). A broad beam super-Gaussian NIR source (800nm wavelength) was simulated.

The % power transmitted using the probe-calorimeter setup was then compared to the % power transmitted using the Monte Carlo simulations. The simulations in the homogeneous skull phantom were used in the form of a lookup table to derive the MC generated fluence using interpolation. The skull thicknesses measured using CT images were used to look up and interpolate the corresponding normalized fluences in the MC
The percentage power transmitted is the normalized fluence on the beam axis at that specific depth multiplied by 100. Figure 6.13 shows the comparison between the transmitted values measured by the probe and those simulated by the Monte Carlo code.

![Figure 6.13 Comparison of % transmitted fluence between the calorimeter-probe measurements and the Monte Carlo. The error bars in the probe measurements represent the maximum and minimum intensities in the 3 averages, while the error bars in the Monte Carlo are the minimum and maximum fluences between the 3 optical models (see table 6.1).](image-url)
Figure 6.14 Comparison of lateral profiles measured using dosimetry probe with the Monte Carlo in water.
Figure 6.15 Boundary conditions simulated using the CT image-guided Monte Carlo.

Figure 6.13 shows that the Monte Carlo simulations compare closely to some of the probe measurement (example points 1-5 in phantom 1) while underestimating the transmission % for other points. Thus Monte Carlo overestimates the attenuation of fluence in the skull, while probe readings show a higher % power transmitted through the skull. The reason behind this difference is due to the differences in the bone density in the skull samples which were not included in the MC simulations. The MC simulations were done in a homogeneous brain phantom and assumed uniform density.
In order to demonstrate the feasibility of using CT image-guided skull boundaries for Monte Carlo simulation, we used the CT images to map the heterogeneity in distribution of bone voxels along with the geometry of boundaries. Figure 6.14 shows the comparison between the lateral fluence profiles (transmitted through the skull immersed in water) measured using the probe versus the Monte Carlo. The boundary conditions derived from the CT images is shown in figure 6.15. The fluence profiles were normalized to the maximum value measured at a depth of 5mm from the inner surface of the skull bone. The results show a close match between the beam spread simulated by the Monte Carlo and measured by the probe. This demonstrates the accuracy with which the scattering properties of the bone were modelled, along with the CT image enhanced boundary conditions. The CT images of the skull sample also show the changing Hounsfield CT numbers across the bone which is the result of varying density of the bone structure. Thus compared to previous studies, we have used the CT images to account for the different optical path lengths along with boundary conditions. We have however, not accounted for the varying densities of the bone, which results in differences between the probe and the Monte Carlo fluences.

6.4 Discussion

The optical transmission study demonstrates the difficulties encountered in optical bone transmission studies. The Monte Carlo can accurately simulate photon attenuation in the skull only when all the optical properties and boundary conditions are simulated correctly. While the skull bone has been measured and modelled as a relatively
homogeneous medium in optical simulation studies, the use of CT images shows that it is far from homogeneous with wide variations in bone densities at different anatomical regions and across subjects. This presents a complicated scenario to model the optical propagation of photons through the skull.

We demonstrated the accuracy of boundary conditions determined using CT images by comparing the lateral profiles between the Monte Carlo and the dosimetry probe. The close match between the profiles shows the accuracy of our simulations. Our study thus also reduced the error in measuring skull thicknesses using calipers, which so often goes unnoticed in complex tissue structure. For example: an error in correctly measuring the skull thickness by a millimeter can result in errors of up to 40% in magnitude (seen from our MC data in figures 6.11, 6.12), depending on the boundary and illumination conditions. Thus any imaging or therapeutic technique needs to reduce the errors due to mismatch in the boundary conditions by using an anatomical imaging technique (such as CT) which can map different tissue boundaries.

To improve the match between the Monte Carlo and the measured fluence in skull models, we hypothesize that using bone density measurement technique such as quantitative CT can significantly improve the localization of high scattering bone voxels in the skull bone. The mapping of Hounsfield values of CT number can be directly linked to the bone density values by imaging bone density phantoms in the CT scanner. This would provide volumetric images of bone densities which can be converted (scaled) to
the corresponding scattering absorption coefficients. The optical coefficient scaling will also need to be calibrated by measuring the optical properties of bone samples of known density.
7 DISCUSSION

7.1 Design and Calibration of Optical Dosimetry Probe

We designed and calibrated an optical dosimetry probe with a linear and isotropic response to input photon fluence. While several designs of the dosimetry probe exist in the medical optics market, the application of a specific dosimetry probe for an application mainly depends on probe sensitivity to the wavelengths of interest. The isotropicity of the dosimetry probes used in past studies is shown in table 7.1. The choice of the titanium dioxide for the probe was made to achieve maximum sensitivity by maximizing scattering near 800nm wavelength through the use of Titanium Dioxide (by Du Pont [71]). We were able to prove that the sensitivity as well as the angular response of the TiO₂ probe is superior to that of the conventional Nylon based probes. The next innovative aspect of our study was the determination of absolute photon fluence from the probe response. By using the linear relationship between the probe and calorimeter responses, along with the experimental derivation of a calibration factor for relating probe response in air to that in water, we were able to derive the mathematical relationship to absolutely quantify photon fluence in tissues for in-vitro or in-vivo studies in the future. This provides a simple technique to quantify probe response experimentally for validation purposes.
Table 7.1 Optical dosimetry probe composition (diameter<2mm) and % isotropicity variation [68, 69].

<table>
<thead>
<tr>
<th>Study By</th>
<th>Probe tip material</th>
<th>Isotropcity Variation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijnissen et al</td>
<td>ArniteTM</td>
<td>11%</td>
</tr>
<tr>
<td>Marijnissen et al</td>
<td>NylonTM</td>
<td>11%</td>
</tr>
<tr>
<td>Van Staveren et al</td>
<td>Helioseal (dental sealant)</td>
<td>20%</td>
</tr>
<tr>
<td>Our study</td>
<td>TiO₂ (best probe)</td>
<td>13%</td>
</tr>
<tr>
<td>Our study</td>
<td>Nylon™ (best probe)</td>
<td>17%</td>
</tr>
</tbody>
</table>

7.2 Dosimetric Validation of a Monte Carlo based Optical Planning tool

The Monte Carlo based tool for photon dose estimation was successfully optimized and validated, using optical dosimetry probe measurements, to study light dose delivery to brain tissue phantoms. Past studies have compared the dosimetry probe measurements with simpler models (non voxelated) of the Monte Carlo along illumination axis in homogeneous phantoms and tissues for simpler (flat or isotropic) beam profiles (flat beams) [104-106]. The long computation times (several hours to days) associated with the Monte Carlo prevented any rigorous approach for validation across diverse tissues and illuminations. To the best of our knowledge, this is the first study which has sought to rigorously validate a 3D voxelated GPU based Monte Carlo using dosimetry probe measurements both along and perpendicular to the illumination axis, in homogeneous and heterogeneous tissue phantoms with independently derived optical properties, and using a complex super-Gaussian beam profile. We also validated the Monte Carlo in a diffuse beam generated by an integrating sphere, thus proving the flexibility of the Monte Carlo in accurately generating different beam profiles.
A past validation study [106] had compared the angular radiance with different viewing angles using a flat cleaved probe to the Monte Carlo in tissue phantoms. The measured versus Monte Carlo fluence showed a % error variation from 0 to 25% (seen from the figure 6 plot in the publication) along the beam axis, mainly due to mismatch in optical properties. In another study [105], Monte Carlo validation using dosimetry in a dissected Pig Bronchus tissue showed higher % mismatch of around 50% at a 4cm depth, with measurement error amounting to 15% variation. The other significant part of the error was accounted for by the variation in estimation of the tissue optical properties and tissue boundaries. This demonstrates the importance of independent validation of optical properties of the medium along with an accurate simulation of boundary conditions in the Monte Carlo. In this study, the average % error was well within 25% for most of our measurements. The acceleration provided by the GPU platform improves the applicability of the Monte Carlo by reducing the development time associated with iteratively optimizing the accuracy of the boundary and illumination conditions, which was difficult to achieve in the CPU based model.

7.3 An Empirical algorithm for preliminary optical dose planning

The brain is a highly heterogeneous structure and has complex distribution of tissues with varying optical properties. In order to target a metastatic site in the brain we need to be able to optimize the light delivery to that region in the brain, which requires us to analyze multiple light source positions, orientations as well as source illumination profiles; all of which affect the path that photons travel through the brain. Since this
requires iterative techniques, multiple simulations of photon propagation with different illumination conditions require a tool which is faster than the Monte Carlo (run time a few hours). Hence an alternative Empirical model with a run time of a few seconds was designed as a preliminary investigation tool with a reasonable level of accuracy compared to the Monte Carlo in heterogeneous tissues.

The Empirical model is based on the photon convolution algorithm and uses weights to simulate photon scatter from one voxel to another. Its 3D voxel based design helps us to integrate it with the Monte Carlo along with 3D imaging modalities such as CT and MR. The empirical algorithm was iteratively optimized with the Monte Carlo and tested in optical phantoms resembling a child’s brain with and without a tumor. We found a reasonable degree of match between the Monte Carlo and the Empirical in both homogeneous and heterogeneous tissues. The lateral profiles in homogeneous phantoms were also compared and were found to match between the two models.

The errors in the Empirical model include boundary conditions which the Empirical is not able to simulate as well as the Monte Carlo. Further research is necessary to investigate and optimize the Empirical algorithm to make it more accurate in complex heterogeneous tissues. Due to its reasonable degree of accuracy, the Empirical algorithm can be used as a preliminary investigation tool to narrow down the optimal illumination conditions while the Monte Carlo can be the Gold standard for the final dose calculation. A comparison of various models used in past studies is shown in table
7.2. The Empirical approach performs favorably with its moderate level of accuracy and fast execution times with respect to Monte Carlo.

Table 7.2 Methods for photon propagation [61, 107-111]. Estimated simulation times for a head study.

<table>
<thead>
<tr>
<th>Method:</th>
<th>Execution time</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPU based Monte Carlo [110]</td>
<td>&gt;24 hours (1-3 days)</td>
<td>Accurate</td>
<td>Long execution times</td>
</tr>
<tr>
<td>GPU based Monte Carlo [61]</td>
<td>4-8 hours</td>
<td>Accurate</td>
<td>Moderate execution time</td>
</tr>
<tr>
<td>Radiative Transport Equation (RTE) [108]</td>
<td>Few minutes</td>
<td>Accurate</td>
<td>Complex to solve</td>
</tr>
<tr>
<td>Diffusion Approximation (DE) [107, 111]</td>
<td>Few seconds</td>
<td>Accurate only at large distances from source, at g&lt;0.6 and at higher albedos (μs/μs+μa)</td>
<td>Errors at short distances from source, at g&gt;0.6 and at lower albedos (μs/μs+μa)</td>
</tr>
<tr>
<td>Hybrid model (MC + DE) [109]</td>
<td>1-3 hours</td>
<td>Moderate accuracy (1-2 std dev)</td>
<td>Moderate accuracy (1-2 std dev)</td>
</tr>
<tr>
<td>Empirical Model [64]</td>
<td>4-12 seconds</td>
<td>Moderate accuracy</td>
<td>Non-analytical technique</td>
</tr>
</tbody>
</table>

7.4 Image guided transmission studies in skull bone phantoms

The NIR transmission study demonstrates the complexities of modelling the optical properties of the skull bone. Past studies measuring the NIR transmission through skulls had measured the transmission through cadaver skulls with intact soft tissues [93, 94]. This resulted in larger uncertainties in the optical properties (with the inclusion of soft
tissue). No image based technique was used in these studies to determine the optical pathlength through the samples. In this study we measured NIR transmission through pure skull bone samples without any soft tissue, and demonstrated the use of image guided technique to determine the bone thickness. We also successfully demonstrated the close match between the lateral beam profiles measured in water, which shows the importance of using image guided techniques to map heterogeneity of the skull. While the transmission errors between the Monte Carlo and the probe measurements are significant for some measurement points, this study tries to point at the scope for future investigation into the heterogeneous density distribution of scatterers in the skull bone. There is a need to model the varying optical scattering of the bone based on bone density. Methods such as bone densitometry and quantitative CT can be used to calculate skull bone densities and can potentially improve the accuracy of the Monte Carlo.
While this study has looked specifically at building optical dosimetry and photon dose simulation tools with an intention of future application in light induced drug activation in the brain, we are still some distance away from accurately modelling the drug release maps in the brain. This is mainly due to a lack of understanding of the mechanism for drug activation. While in vitro experiments as well as in vivo studies in mice have shown promising results, the energy threshold for drug release is still uncertain. The drug-nanocomplex molecule consists of a therapeutic drug molecule (e.g. lapatinib) which is complexed with a gold plated silica nanoshell [8]. These nano-complexes are incubated in macrophages and monocytes and injected into the blood stream, cross the blood brain barrier, and accumulate in the metastatic lesions in the brain [8, 9]. Thus when irradiated with an NIR source with sufficiently high power, the high absorption cross-section of gold nanocomplexes results in heating of the nanoparticles [86, 87] which can lead to breakage of bonds binding the drug (or any fluorescent molecule) to the nano-complex and subsequent release and activation of the drug [8, 9]. The resulting rise in temperature has been shown to be around 37.4°C as shown in previous studies [86] for a power of 4W/cm². The heating property of the gold nanoshell nano-complex can be
tuned by changing the size of the silica nano-shell compared to that of the outer gold plated layer [88], which allows us to optimize the drug molecule with respect to the wavelength of light delivery. While this shows significant promise in the mechanism of temperature rise leading to drug release, more research needs to be done to understand the temperature related dependence of the drug release.

In order to control the rise in temperature in the region surrounding the nanocomplex molecules, the instantaneous energy provided to a tissue region can be controlled by adjusting the pulse width of the laser beam. The use of pulsed laser beams has been shown to improve the instantaneous temperature rise and release in of drug molecules tethered to nanoparticles, compared to continuous wave lasers [112]. This will allow more instantaneous power to be coupled to the nano-molecules while reducing the chances of laser induced adverse tissue heating or denaturing of the drug. The maximum energy that can be safely coupled to tissues is limited by the maximum permissible exposure (MPE). MPE values are based on the pulse duration and the tissue type [113, 114]. For example, if we use a laser beam of 1 ns pulse duration, the MPE to the skin is 3.17x10^7 W cm^{-2} [113, 114]. Based on our prior Monte Carlo simulations using a flat 2cm diameter beam, the amount of power coupled to the soft tissue for 1.1cm and 0.2cm thick adult and neonatal skull is 4.3x10^5 W cm^{-2} and 1.5x10^7 W cm^{-2}, respectively. Thus, a therapeutic drug molecule needs to be designed such that it can be activated at a threshold less than the maximum permissible power coupled to tissues at a specific depth. For example, a drug molecule with an energy threshold of 1 Wcm^{-2} can
be released up to a depth of 3.8cm in the white matter of an adult brain (skull thickness 1.1cm, gray matter thickness 2cm), and up to 4.6cm in a neonatal brain (skull thickness 0.2cm, gray matter thickness 0.2cm) for a flat beam of 2cm diameter, 1ns temporal spread and an input fluence of $3.17 \times 10^7$ W cm$^{-2}$. This shows that the structure of the brain and path lengths through the tissue can significantly impact the fluence coupled and the effectiveness of therapy. However, these results demonstrate the feasibility of NIR stimulated drug release, in particular for children where 4.6cm is more than half the diameter of the brain cavity.

Even though reducing the laser pulse width can enhance drug release without denaturing the drug or heating the tissue, it can also significantly impact the instantaneous or peak energy fluence within the brain. Multiple scattering in brain tissues causes the photons to travel with different optical path-lengths, thus simultaneously increasing the pulse width and decreasing the peak power at greater depths. Past studies have measured the temporal dispersion of laser beams in scattering tissues by using time of flight method with a fast optical detector [115, 116], or by using radio frequency (RF) modulated light source by detecting the phase of transmitted light [117, 118]. A theoretical basis of calculation of the temporal point spread function is also provided by Arridge [115] using the temporal point spread function (TPSF), while the TPSF is the “response function (Green’s Function) of the medium to a delta impulse” [115]. The Monte Carlo used in this study has the ability to simulate photon pulses with user-defined pulse duration. In our MC simulation studies, we calculated the temporal
dispersion of a 1ns laser beam by measuring the full width at tenth maximum of the laser pulse as it propagated along a circular head phantom (boundary conditions shown in figure 5.11). The plot of temporal pulse width to the depth in the tissue is displayed in figure 8.1. The pulse width is seen to increase by 4-5 times at depths of 3-5cm. This implies a reduction in the fluence per unit time by approximately this same amount. The pulse width was measured by calculating the full width at tenth maximum, a quantity which determines the pulse duration up to 10% of maximum fluence. Therefore, some care must be taken when considering the pulse width in the design of the treatment plan. To date, the Monte Carlo can be used to predict this spread to optimize drug release. Further temporal convolution methods may need to be added to the empirical model.
Figure 8.1 MC simulation of temporal pulse width versus depth in a heterogeneous head phantom (see figure 5.11) for an input pulse 1ns wide. The pulse width was measured by calculating the Full Width at Tenth Maximum (FWTM) to analyze the temporal beam spread.

There is a need to quantify the errors due to variability of brain tissue properties, particularly the skull bone between different patients. The skull bone thickness and density varies across different anatomical regions of the brain [89]. The optical properties of the skull bone are also seen to vary across samples [89], which can result in differences between the estimation and delivery of photon fluence to metastatic tissue in the brain. Hence the need for using a medical imaging system such as Computed Tomography (CT) is necessary to segment tissues in the brain, especially the bone-brain interface. In our study the average % error in determining bone thickness
measured using versus a scale was 30%. Thus modelling the skull heterogeneity using CT images has the potential to reduce simulation errors of up to 73% in the fluence coupled to soft tissue in adult brains and up to 20% in neonatal brains with respective skull thicknesses of 1.1 cm and 0.2 cm.

While the bone-brain interface is clearly visible using CT images, better soft tissue contrast is necessary to segment different soft tissues such as white matter, gray matter, cerebrospinal fluid and metastatic lesions (if any) in the brain. This is best done using Magnetic Resonance Images (e.g. T2-weighted), which are also used as the standard imaging protocol to segment metastatic lesions in the brain [90]. The MR images however cannot be used to image the bone-brain interface, as bone images of the brain are generally poor. Hence there is a need to super-impose and co-register CT and MR images of patients about to undergo optical therapy. This would provide a significant improvement in brain tissue segmentation over CT-only or MR-only based imaging and segmentation methods. The co-registration software (e.g. Gamma Plan [91, 92]) used needs to be highly accurate to ensure minimal errors in boundary conditions which need to be accurately depicted by the Monte Carlo. Phantom studies to determine image registration accuracy [92] can be done to quantify any errors related to inaccurate tissue boundaries.
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Appendix A  Validating Scattering Coefficient of Intralipid through Probe Measurements

In order to validate the scattering properties of the intralipid solution and further validate the results from the spectrophotometer based studies, we used the dosimetry probe and Monte Carlo to derive the reduced scattering coefficient of the intralipid solution. Different concentrations of intralipid were illuminated in Plexiglas cuvette using the diffuse broad beam from the integrating sphere (connected to the laser source). The fluence was measured by the dosimetry probe along the beam axis for each of the solutions. We then used the Monte Carlo to derive the scattering coefficient at which the probe measurements match the Monte Carlo along the beam axis for the same illumination and boundary conditions. The absorption coefficient of intralipid was assumed to be the same as of water and the anisotropy factor of 0.636 was used in the Monte Carlo. The results are close to those obtained by the spectrophotometer method and are shown in figure 4.

This form of measurement was an additional validation step to the spectrophotometer method. This method however needs to be precisely calibrated as additional errors and offsets may be caused due to mismatch in boundary conditions as well as small differences in illumination profiles between the MC and probe measurements.
Figure 1 The scattering coefficient of intralipid measured using probe measurements in various concentrations of intralipid and correlated with MC simulations.
We validated the 3D Photon dose profiles in a goat skull phantom (figure 2). A goat skull (dry skull bone) was filled with an intralipid solution to resemble brain tissue. The power transmitted was measured to be 5.2% while MC simulations showed 3.2% transmission. The normalized MC and probe measurements within the phantom show identical profiles both along (figure 3) and perpendicular to the beam axis z (figure 4).

Figure 2 Experiments with a goat skull phantom to measure optical fluence distribution.
Figure 3 Experiments with a goat skull phantom to measure optical fluence distribution.

Figure 4 Experiments with a goat skull phantom to measure optical fluence distribution.
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