Evaluation of Forward Models for Time-Domain and Small-Scale Diffuse Fluorescence Tomography

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Abstract

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Diffuse Optical Tomography (DOT) and Diffuse Fluorescence Tomography (DFT) are emerging non-invasive imaging modalities for a range of clinical and pre-clinical applications. In DOT and DFT, forward modeling of light propagation through biological tissue between source and detector pairs plays a crucial role in image reconstruction. Two major methods for computing forward models have emerged in the literature: i) the diffusion approximation to the Boltzmann Transport Equation and, ii) Monte Carlo simulations. It is generally accepted that Diffusion Theory is less accurate than Monte Carlo methods. However, Monte Carlo models can require impractically long computation times (even with modern hardware acceleration), whereas Diffusion Theory computes extremely rapidly. As such we are interested in this speed-accuracy trade off, and in particular with respect to DFT technologies under development in our lab. In this thesis, we evaluated Diffusion Theory and two Monte Carlo based methods (the Adjoint and Photon Tracking methods) for computing forward models for time-domain DFT and small-scale DFT.

We studied the agreement between these methods for a range of instrument geometries, pathlengths and time-points following a simulated laser pulse. Our results indicate that Jacobian functions through bulk tissue computed with Diffusion Theory generally agreed well with Monte Carlo methods under the conditions tested, with the exception of at very early time points following a laser pulse (about 5% of maximum on the rising edge of the transmitted time-resolved curve), for very large source-detector angular offsets and for very small geometries. As expected, greater inaccuracies were observed very close (within ≈ 10 transport mean-free-paths) to sources and detectors. Minor differences between the Monte Carlo Adjoint and Monte Carlo Photon Tracking methods were also identified for specific conditions with very small imaging volumes (on the order of 3 mm) and at extremely early time points following a laser pulse. As such, we conclude that for our DFT imaging problems Diffusion Theory is a valid and computationally efficient method for computing Jacobian functions under nearly all practical circumstances. Future studies include extension of this work to more complex geometries and a broader range of optical properties. The effect of minor disagreements in computed forward models on the inverse image reconstruction problem is also the subject of ongoing work.
I am indebted to many people toward the completion of my Master study. I can not imagine that I could finish my research and thesis without their guidance and support. Instead, because of their generous help, I found this journey full of surprises and joyance.

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I also wish to thank my wonderful team members for their friendship and help. It is my pleasure to work with all of them.

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## Contents

**Abstract**

**Acknowledgements**

**List of Figures**

**List of Tables**

### 1 Introduction

1.1 Diffuse Optical Tomography and Diffuse Fluorescence Tomography 2

1.2 Forward Problem

1.2.1 Diffusion Theory 5

1.2.2 Monte Carlo Method 6

1.3 Time-resolved and Small Geometry Forward Model

1.3.1 Time-resolved Forward Model 8

1.3.2 Forward Model in Small Geometries 10

1.4 Purpose 11

### 2 Methods

2.1 Diffusion Theory Forward Model 13

2.2 Monte Carlo Forward Model

2.2.1 Simulation Principle 17

2.2.2 Mesh-base Monte Carlo Introduction 18

2.2.3 Monte Carlo Method 1 - Adjoint Method 20

2.2.4 Monte Carlo Method 2 - Photon Tracking 21

2.3 Description of Geometry and Optical Property

2.3.1 Semi-infinite Slab Geometries 23

2.3.2 Cylindrical Geometries 25

2.3.3 Irregular Geometries 25

2.3.4 Optical Properties 27

2.4 Metrics for Comparison of Forward Models 27

### 3 Results

3.1 Slab Geometries 31
Contents

3.1.1 Time-resolved forward model .................................................... 31
  3.1.1.1 TPSF Analysis ................................................................. 32
  3.1.1.2 Large Slab Geometries: Diffusion Theory vs the MC-Adjoint Method ... 36
  3.1.1.3 Small Slab Geometries: Diffusion Theory vs the MC-Adjoint Method ... 37
  3.1.1.4 Slab Geometries: MC Adjoint vs. MC Photon Tracking Methods ........ 38
3.1.2 Continuous Wave Sensitivity Functions ......................................... 42
3.2 Cylindrical Geometries ................................................................... 43
  3.2.1 Cylindrical Geometries: Diffusion Theory vs the MC Adjoint Method ...... 43
  3.2.2 Cylinder Results: MC Adjoint vs. the MC Photon Tracking Method ........ 47
3.3 Irregular Geometry ........................................................................ 49
3.4 Half and Double Optical Properties in 2cm Slab ................................... 51

4 Discussion and Conclusions .............................................................. 54
  4.1 Discussions ................................................................................. 54
  4.2 Future Work ............................................................................... 58
# List of Figures

1.1 DOT imaging ................................................. 3
1.2 DFT example ............................................... 4
1.3 Early Photons Propagation .............................. 8
1.4 Early Photons FWHM reduction ....................... 9
1.5 Early Photons SNR ......................................... 10
1.6 Diffuse Fluorescence Flow Cytometry System Diagram .... 11
1.7 Diffuse Fluorescence Flow Cytometry Reconstruction in vivo ... 12

2.1 Green Function ............................................. 15
2.2 Diffuse Equation Sensitivity Matrix .................. 16
2.3 Mesh of Mouse Head ..................................... 19
2.4 MMC Configuration File ................................. 20
2.5 Adjoint Method Sensitivity Matrix .................... 21
2.6 Photon Tracking Sensitivity Matrix ................. 23
2.7 Slab Model ............................................... 24
2.8 Cylinder Model .......................................... 26
2.9 Irregular Geometry ....................................... 26
2.10 FWHM .................................................. 28
2.11 Contour ................................................ 29

3.1 Large Slab Metrics ....................................... 33
3.2 Small Slab Metrics ....................................... 34
3.3 Unreasonable Weight Matrix ........................... 39
3.4 Forward Model with Replaying Different Numbers of Photons ... 40
3.5 Contours in Large Size Cylinder ..................... 44
3.6 Contours in Small Size Cylinder ...................... 45
3.7 2cm Cylinder Overlap vs Detector Placements .... 46
3.8 5mm Cylinder Overlap vs Detector Placements .... 46
3.9 Overlap vs Cylinder Size ............................... 47
3.10 Photon Tracking vs Adjoint Method in 3mm Slab .......... 48
3.11 Irregular Contours ..................................... 50
3.12 Half Optical Properties in 2cm Slab .................. 52
3.13 Double Optical Properties in 2cm Slab ............... 53
# List of Tables

1.1 Advantages and Disadvantages in Diffusion Theory and Monte Carlo ........................................ 7

2.1 Timebin Sizes of Photon Tracking ........................................................................................................ 25

3.1 TPSF Point in 2cm Slab .......................................................................................................................... 35
3.2 TPSF Point in 1cm Slab .......................................................................................................................... 35
3.3 TPSF Point in 5mm Slab .......................................................................................................................... 35
3.4 TPSF Point in 3mm Slab .......................................................................................................................... 36
3.5 Time Point Deviation (DT vs MC-Adj) .................................................................................................... 37
3.6 2cm Slab Agreement Time Table (DT vs MC-Adj) ................................................................................. 37
3.7 1cm Slab Agreement Time Table (DT vs MC-Adj) ................................................................................. 37
3.8 5mm Slab Deviation Table (DT vs MC-Adj) .......................................................................................... 38
3.9 3mm Slab Deviation Table (DT vs MC-Adj) .......................................................................................... 38
3.10 2cm Slab Agreement Time Table (MC-Adj vs MC-PT) ....................................................................... 40
3.11 Numbers of Photo Captured in 2cm Slab around Deviated Time ....................................................... 41
3.12 1cm Slab Agreement Time Table (MC-Adj vs MC-PT) ....................................................................... 41
3.13 Numbers of Photo Captured in 1cm Slab around Deviated Time ....................................................... 41
3.14 5mm Slab Agreement Time Table (MC-Adj vs MC-PT) ....................................................................... 41
3.15 Numbers of Photo Captured in 5mm Slab around Deviated Time ....................................................... 41
3.16 3mm Slab Agreement Time Table (MC-Adj vs MC-PT) ....................................................................... 41
3.17 Numbers of Photo Captured in 3mm Slab around Deviated Time ....................................................... 41
3.18 2cm Slab Deviation in CW Table ......................................................................................................... 42
3.19 1cm Slab Deviation in CW Table ......................................................................................................... 42
3.20 5mm Slab Deviation in CW table ......................................................................................................... 43
3.21 3mm Slab Deviation in CW Table ......................................................................................................... 43
3.22 2cm Cylinder Overlap (MC-Adj vs MC PT) ......................................................................................... 48
3.23 1cm Cylinder Overlap (MC-Adj vs MC PT) ......................................................................................... 49
3.24 5mm Cylinder Overlap (MC-Adj vs MC PT) ......................................................................................... 49
3.25 3mm Cylinder Overlap (MC-Adj vs MC PT) ......................................................................................... 49
Chapter 1

Introduction

Diffuse Optical Tomography (DOT) and Diffuse Fluorescence Tomography (DFT) are emerging clinical and pre-clinical optical imaging modalities. However, biological tissue is inherently highly scattering to light. As discussed in this chapter, is generally understood that accurate computation of light propagation in biological tissue (“forward models”) is important for obtaining robust image reconstructions in DOT and DFT. The most exact equation for modeling light propagation in an absorbing and scattering media is the Radiative Transport Equation (RTE). However, the RTE has six independent variables and requires detailed modeling of light scattering; therefore, it is difficult to implement in all but the simplest situations. The diffusion approximation to the RTE (diffusion equation) is greatly simplified and computes the forward model rapidly, but is widely accepted to be less accurate in specific situations due to a number of simplifying approximations that are made. Monte Carlo models of light propagation are significantly more accurate that the diffusion equation, but are computationally very expensive. In specific cases, Monte Carlo method may take several days to solve a forward problem between source-detector pairs, even on modern computers with hardware acceleration. Moreover, different MC methods have been described in the literature, which have particular computational trade-offs and may yield more or less accurate solutions in specific circumstances. Therefore, DOT and DFT engineers, including our group, are concerned
with the trade-off between forward model accuracy and computational cost. In practice, significant time and computational resources may be expended unnecessarily if diffusion theory and Monte Carlo forward models agree under the specific imaging conditions of interest.

In this chapter, we will first briefly review the underlying mathematics and principles of DOT and DFT, and then introduce two specific DOT and DFT problems of particular interest in our group: time-resolved forward modeling and forward model in small geometries. For nearly all metrics we considered, diffuse theory and Monte Carlo method agreed with less than 10% error - except in special circumstances such as very early time points or in very small geometries with large angular offsets - despite the many simplifications made. This was unexpected. Implications for these results in our work and others are discussed.

1.1 Diffuse Optical Tomography and Diffuse Fluorescence Tomography

Diffuse optical tomography (DOT) is an optical imaging techniques that images bulk ("macroscopic") biological tissues in a diffusive regime. DOT generates images of the contributions of different optical properties [1] [2] such as scatter and absorption. DOT is a non-invasive and in vivo biomedical imaging technique which has rapidly developed in recent years. Applications of DOT include detecting tumors in breasts, imaging of hemodynamic activity and hematomas in brains. The principle of the applications is that greater flows of blood make tumors or activated areas on the brain more oxygenated compared to surrounding tissues, which provides a target absorption inhomogeneity to image[2]. Figure 1.1 shows an example of the placements of laser and the reconstructed image[3].

Diffuse Fluorescence Tomography (DFT) has likewise emerged as a significant tool in biomedical research to investigate molecular and cellular processes in limbs, organs or whole animals in vivo [4]. Sophisticated
fluorescent labeling strategies enable fluorophores to be selectively targeted to specific tissue types and therefore imaged by fluorescence contrast. For instance, for cancerous tissue, certain types of protein and gene expression can be specifically labeled by appropriate biomedical markers [4] [5] [6] [7]. Figure 1.2 is an example of a reconstructed image of lowest and highest concentrations of fluorescence signal [8].

1.2 Forward Problem

In both DOT and DFT imaging there are two specific computational problems, the forward problem and the inverse problem. In this section, an introduction to the forward problem and descriptions of methods for solving it will be presented. In general, “forward models” model photon propagation in turbid media between source-detector pairs. In physical experiments, tissue is illuminated by narrow near-infrared light
from various positions, and reemitted light from tissue is measured by an array of detectors at different positions. To obtain an image reconstruction, a model of re-emitted light propagation is required. This is generated using a model of light propagation in diffusive tissue and presumed optical properties of the tissue (scattering, absorption and scatter anisotropy) [1] [2] [9] [10] [11] [12]. Physically, the forward model is the fluence distributions in diffusive media between a source-detector pair. In the DOT and DFT literature these are often referred to as “sensitivity functions”, “weight functions”, “Jacobians” or colloquially “Banana functions”. An accurate forward model in diffusive media is generally accepted to yield more accurate image reconstructions. In principal, the most accurate method of computing light propagation in tissue is using the Radiative Transport Equation (RTE). However, the RTE requires 6 independent variables as well as detailed knowledge of photon scatter angular distributions (“phase functions”) and therefore is of limited use in practice. Two methods are commonly used to model light propagation in scattering media between source-detector pairs. One method is to use the diffusion approximation to the RTE (using either an analytic or numerical solution), and the other is to use a Monte Carlo method, which is a direct numerical implementation of the RTE [1] [11] [12].
1.2.1 Diffusion Theory

Diffusion theory (DT) is an approximation of the RTE which allows rapid computation of Jacobians. However, the assumptions and approximations mean that DT is less accurate under a number of circumstances. First, in order to accurately apply DT, scattering effects must be dominant over absorption within a diffusive medium. Also, scattering is modeled by reduced scattering coefficient ($\mu_s' = \mu_s(1 - g)$, where $\mu_s$ is scattering coefficient and $g$ is anisotropy factor), which means that information about the scattering phase function is lost. Moreover, all light sources are considered to be isotropic, so it lacks of directional properties at the positions near sources and detectors. Furthermore, DT is most accurate away from boundaries, since there is a large change in photon current. As a result of the drawbacks mentioned above, it is generally accepted in the DOT and DFT imaging fields that DT is not accurate in small geometries, and at early times following a light pulse. Klose et.al. proposed a simplified spherical harmonics ($SP_N$) model (as apposed to the P-1 approximation in DT), which has been reported to significantly improve accuracy versus DT in small geometries and highly light absorbing medium [13]. Similarly, Dehghani’s group images small animals in good quality with an $SP_N$ based forward model, and they claim that $SP_N$ models photon propagation more accurately where DT is less valid [14]. In addition, Intes et. al. support that the time-resolved Monte Carlo technique is accurate in large span of optical properties, small geometries and geometries with complex boundaries [15]. However, on the other hand, Holt and Pogue have performed time-resolved DFT imaging in NIRFAST using a numerical diffusion theory solver [16]. Our previous experimental data also suggest that DT is quite accurate in modeling time-resolved and small geometry imaging.

Overall, the exact parameters of agreement (object size, timepoint following the laser) or magnitude of disagreement are poorly defined in the literature and are still a point of debate in the field. Due to the significant computational benefits of using DT (i.e. it computes extremely rapidly), we were interested in
studying this question for two DFT problems of specific interest in our lab.

1.2.2 Monte Carlo Method

As an alternative to solving the forward problem by the diffusion equation, the Monte Carlo (MC) method provides another strategy to model the forward problem. MC numerically simulates photon propagation in biological tissue by generating a series of pseudo-random numbers for photon random walk [1]. Physically, photon propagation is a series of random events, including absorption, scattering, transmittance and reflectance. The MC method constructs a stochastic model in which the expected value of a certain random variable is determined by optical properties. The expected value is estimated by averaging multiple independent photons. Due to statistical nature, MC method requires a large number of photons to obtain a meaningful result, which is computationally time-consuming. Each photon’s trajectory is governed by four optical properties, which are absorption coefficient ($\mu_a$), scattering coefficient ($\mu_s$), anisotropy ($g$) and refractive index ($n$). A number of different MC approaches for computing Jacobian have been described in the literature. Two of particular interest for this thesis are the adjoint method (MC-Adj) and the photon tracking (MC-PT). Briefly, the MC-Adj calculates weights by a multiplication between two independent simulations of light propagation from source side and detector side based on the principle of reversibility of light. MC-PT works by reconstructing the path of photons launched from a source position that arrive at a particular detection point. Since MC-Adj and MC-PT are both MC based models, they have good agreements in most circumstances. However, because of the different mechanism of modeling photon propagation, the differences still exist, especially in small geometries and at very early time. First, in small geometry, incident light has more effect on the forward model, so the MC-Adj forward model is more like two pencil-beam incident lights intersecting in the diffusive medium, whereas, MC-PT models are more smooth in fluence distribution. Second, MC-PT is very expensive in computation at very early time due to very few photons detected, so a statistically useful forward model requires an extremely large
number of photons launched. Third, MC-Adj models detectors as pencil-beam, whereas MC-PT detectors accept photons over a finite solid angle. The differences of modeling detectors cause the different photon propagation near detectors in the diffusive medium.

The MC method is believed to be reliable for the forward problem, because it is a physically intuitive technique and a direct numerical implementation of the RTE and therefore works in most situations without the assumptions in diffusion equation. However, as noted above, MC is very computationally expensive compared to DT. In order to get a statistically meaningful forward model, MC method requires a large number of photons to be launched in diffusive medium, particularly for studying photon propagation in large tissue volumes or at very early or very late times following a laser pulse. As discussed in more detail in Chapter 2, a number of MC software packages are available to investigate photon transportation in diffusive medium, such as MCML [1], MC321 [17], MCX [18] and MMC [19]. Table 1.1 shows the advantages and disadvantages of DT and MC forward model respectively.

<table>
<thead>
<tr>
<th>Method</th>
<th>Modeling type</th>
<th>Computation Speed</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT</td>
<td>Analytical/Numerical</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>MC-Adj</td>
<td>Statistical</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>MC-PT</td>
<td>Statistical</td>
<td>Low</td>
<td>High</td>
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1.3 Time-resolved and Small Geometry Forward Model

In this section we discuss two specific DFT applications that are of particular interest in our group: modeling of light propagation through bulk tissues at early times following a short laser pulse, and modeling of light propagation in a very small (2-3 mm diameter) geometries. The motivation for these studies are
described briefly here.

1.3.1 Time-resolved Forward Model

As noted, the high degree of light scattering during photon propagation through diffusive medium results in an ill-posed inverse problem in image reconstruction. In recent years, a number of groups have proposed and demonstrated early photons transmitted through the media can decrease light scattering, which improves image reconstruction quality. Since early arriving photons have fewer scattering events, early photons propagate along more direct path between a source-detector pair [20] [21] [22] [23], as shown in Figure 1.3

![Figure 1.3: Light propagation in biological tissue. a) Early Time Gate photon, 5% - 10% of the peak intensity; b) un-gated quasi-CW photon.](image)

From experiments conducted by our team, early photons reduce photon scattering- characterized by the full width at half maximum (FWHM) of photon density spread function (PDSF)- by up to 60% versus un-gated, CW measurements. Time-resolved MC shows that the transmitted early photons had undergone
about 1/3 of the number of total scattering events compared to CW photons. As a result, it provides a general guideline for selecting an early time gate, namely, how much reduction in scattering can be achieved [24], as shown in Figure 1.4:

![Figure 1.4: The FWHM of the PDSF as a function of measurement time. Reduction of PDSF FWHM of more than 50% was observed for early photons versus quasi-CW photons.](image)

On the other hand, measurement of early photons implies rejection of more than 99% of all photons transmitted through the media. The noise in performance of an early photon imaging system is reduced versus a comparable CW system. In our recent work by Valim et al., [24], early photon measurement has reduced signal to noise properties by as much as 15dB- compare to CW measurement under typical condition. The lower signal to noise ratio is as shown in Figure 1.5:

However, MC method calculations with either MC-PT or MC-Adj at very early times (i.e. less than 10% rising edge of the time-resolved transmitted photon density curve) through several centimeters of diffusive media is very computationally expensive since it requires launching a very large number of photon packets.
Figure 1.5: SNR at different time gates for 0.2-s and 1.0-s acquisition times. In both cases, the photon counting rate was $10^6$ photons/s.

(more than $10^6$ photons in our experiment) to yield useful results. DT computes much more rapidly, but MC method and DT agreement in the early-time regime is an open question in the field.

1.3.2 Forward Model in Small Geometries

We have also performed fluorescence tomographic imaging of small single circulating cells in the limbs of small animals using a technique called “diffuse fluorescence flow cytometry” (DFFC). Previous work in our lab has shown that it is possible to detect fluoreoscently-labeled cells in a 2-3 mm mouse limb (tail or hindleg), and to reconstruct their positions with 100µm accuracy. The Figure 1.6 shows an DFFC system diagram in our group [25]. Figure 1.7 is an example of reconstruction in vivo [25].
We have significant interest in performing DFT in small tissue volumes with diffuse light. However, modeling photon propagation in small geometries remains a challenge. Specially, we hypothesized that for sufficiently small geometries (on the order of a few transport mean free paths, $\frac{1}{\mu_s + \mu_a}$) the MC-Adj may not be appropriate due to the directionality of the detector which is normally assumed negligible. In addition, our previous work where we used DT to compute weight functions and reconstruct the cell positions for small geometric yielded surprisingly accurate results, and therefore we also questioned the generally held assumption that DT was inappropriate to use in tomography applications for very small geometries.

**Figure 1.6:** (a) Schematic of the DFFC instrument showing the two-laser modulated illumination scheme (inset). (b) Photograph of the DFFC during *in vivo* operation. The positions of the six detectors and two light sources are indicated.

### 1.4 Purpose

As discussed above, we are interested in establishing a trade-off between accuracy and computation cost in calculating forward model for different circumstances. Therefore, in the present work we compare DT forward models and MC forward models, and investigate how the three methods (DT, MC-Adj and MC-PT) perform in two specific circumstances.
Figure 1.7: Data acquired for uninjected mice ((a),(b)) and for a mouse where 105 Vybrant-DiD labeled MM cells were injected retro-orbitally ((c),(d)) when the rst ((a),(c)) and second ((b),(d)) lasers were illuminating the tail of a nude mouse. The red arrows in (c),(d) indicate the time of injection. A cross-sectional image of the tail of a mouse (obtained post-mortem) (e), indicating the position of the major blood vessels including the VA, LV and DV. The diameter was about 3 mm. For these experiments, the mouse was placed on its side, so that laser 1 directly illuminated the VA. Example reconstructions of circulating cells, corresponding to spikes detected at (f) 1350, (g) 1371, (h) 1714, (i) 1819 and (j) 1939 s. As above, the centroid of each reconstruction is marked with a green circle.
Chapter 2

Methods

In this chapter we describe our experiments designed to compare and characterize the three methods for computing the forward model outlined in the introduction: DT, MC-Adj and MC-PT. We calculated forward models with each method in different geometries, including slab geometries with different thicknesses and source-detector pair placements, and in cylinders with different diameters and source-detector pair placements. We computed these as functions of time following an infinitely short laser pulse. To characterize these, we selected 3 specific metrics to qualify the agreement and disagreement between the three forward models as described below.

2.1 Diffusion Theory Forward Model

The diffusion approximation is obtained by applying a number of simplifying assumptions to Radiative transfer equation (RTE). The RTE is an explicit model of light transport in scattering and absorbing media and analytically models photon transportation as [1]:

\[ \n\]
\[ \frac{\partial L(\vec{r}, \hat{s}, t)}{c \partial t} = -\hat{s} \cdot \nabla L(\vec{r}, \hat{s}, t) - \mu_t L(\vec{r}, \hat{s}, t) + \mu_s \int_{4\pi} L(\vec{r}, \hat{s}', t) P(\hat{s}' \cdot \hat{s}) d\Omega' + S(\vec{r}, \hat{s}, t) \]  

(2.1)

which means the change in energy in the volume element with in the solid angle element per unit time, \( \frac{\partial L(\vec{r}, \hat{s}, t)}{c \partial t} \), is composed of 5 contributions which are Divergence \( (\hat{s} \cdot \nabla L(\vec{r}, \hat{s}, t)) \), extinction \( (\mu_t L(\vec{r}, \hat{s}, t)) \), scattering \( (\mu_s \int_{4\pi} L(\vec{r}, \hat{s}', t) P(\hat{s}' \cdot \hat{s}) d\Omega') \) and source \( (S(\vec{r}, \hat{s}, t)) \).

The diffusion equation is a simplification (approximation) of the RTE and is frequently used to model photon propagation in biological tissue. The diffusion approximation is derived from three basic assumptions: first, \( L(\vec{r}, \hat{s}, t) \) is expanded to the first order (\( P_1 \) approximation); second, source is isotropic such that it is modeled as \( S(\vec{r}, \hat{s}, t) = \frac{S(\vec{r}, t)}{4\pi} \); third, the fractional change in current density \( \vec{J}(\vec{r}, t) \) is negligible over one transport mean free path. The simplified diffusion equation is as follows:

\[ \frac{\partial \Phi(\vec{r}, t)}{c \partial t} + \mu_a \Phi(\vec{r}, t) - \nabla \cdot [D \nabla \Phi(\vec{r}, t)] = S(\vec{r}, t) \]  

(2.2)

where, \( \Phi \) is the fluence rate, \( c \) is the speed of light in the scattering medium, \( \mu_a \) is the absorption coefficient, \( D = \frac{1}{3(\mu_s + \mu_a)} \) is the diffusion coefficient and \( S \) is the source power density.

In DOT and DFT, the forward problem relates source-detector measurements to physical positions inside the medium. To compute the “weight function” between a source and detector pair, the forward problem is frequently linearized, separating the object (target) and Green’s functions describing light propagation in the diffusive media:

\[ [U_{se}] = [W][\delta \mu_a] \]  

(2.3)
Likewise $[W]$ is frequently computed using the Green’s theorem method as follows:

$$W(\vec{r}_s, \vec{r}_d) = \int U_0(\vec{r}, \vec{r}_s) G(\vec{r}_d, \vec{r}) d\vec{r}$$  \hspace{1cm} (2.4)$$

where $\vec{r}_s$ and $\vec{r}_d$ are positions of source and detector, respectively, $r$ is a position in diffusive medium. The Green function’s $G$ and $U_0$ are given by the solution to the steady state diffusion approximation to the RTE:

$$G(\vec{r}) = \frac{\exp\left(-\frac{\mu'_s}{4\pi D} r^2\right)}{4\pi D r^2}$$ \hspace{1cm} (2.5)$$

$$U_0(\vec{r}) = \frac{B \exp\left(-\frac{\mu_s}{4\pi D} r^2\right)}{4\pi D r^2}$$ \hspace{1cm} (2.6)$$

where, $D = \frac{1}{3(\mu'_s + \mu_a)}$, $\mu'_s$ is reduced scattering coefficient, $\mu'_s = \mu_s(1-g)$. $B$ is a constant related to incident light.

The physical meaning of the Green function method is represented in Figure 2.1. $U_0(\vec{r'}, \vec{r}_s)$ shows the light propagating from the source to a point inside the medium; $U_0(\vec{r'}, \vec{r}_s)O(\vec{r'})$ is a new “scattered” source for the light propagation to the detector; $G(\vec{r}_d, \vec{r})$ describes the propagation.

![Figure 2.1: Illustration of Green’s theorem method](image)

In time-resolved mode, the weight function between a source detector pair as a function of time following
a very short (impulse) light pulse is given by [20]:

$$W(r_s, r_d, t) = \int \int_0^t U_0(r_s, t, \tau) G(r_d, r, t - \tau) d\vec{r} d\tau$$  \hspace{1cm} (2.7)$$

where weight function at \( t \) is calculated by a time convolution, with integrating variable \( \tau \). Here, the time-dependent Green’s function is derived by time dependent diffusion approximation (TDDA)[26]. The TDDA solution for photon propagation from a short light pulse in an infinite diffusive medium is:

$$\Phi(\vec{r}, t) = \frac{1}{(4\pi Dct)^{3/2}} exp\left(-\frac{\vec{r}^2}{4Dct}\right) exp\left(-\mu_a t\right)$$  \hspace{1cm} (2.8)$$

Figure 2.2 shows an examples of diffusion equation weight matrix in CW mode and time-resolved mode. The geometry is semi-infinite slab with 2cm thickness. Each grid in the figure represents 0.25mm-by-0.25mm.

---

**Figure 2.2:** Examples of diffusion equation sensitivity matrix. (Left) CW sensitivity matrix (Right) Time-resolved (210ps) sensitivity matrix
As discussed in Chapter 1, analytically computing the forward problem using the diffusion approximation to the RTE is a fast and computationally inexpensive method. However, the assumptions made in the derivation from RTE may lead an inaccurate forward model. In particular, at very early time when photons just scatter a few times, photons are likely to travel along the incident pulse light direction in majority, so it is inappropriate to assume photons’ directions are isotropic in the diffusion equation. In small geometries, photons will be captured by detectors with a few scattering events, so incident pulse light direction affects forward model. Therefore, we assume that isotropic source may lead to a different results. From Alfano’s research, diffusion theory may fail when $\frac{z}{l_t}$ is small, where $z$ is the thickness of diffusive medium, and $l_t$ is photon mean free path [27]. In this work we made the further simplification that boundary effects are neglected when computing weight functions with DT, although in general this is impossible. With the drawbacks mentioned, MC is considered to be more accurate in modeling photon propagation. However, as we show, even with these simplifying assumptions we were able to obtain surprisingly good agreements under most of the conditions we considered.

2.2 Monte Carlo Forward Model

2.2.1 Simulation Principle

Photon propagation in biological tissue can be modeled as a series of random events, including absorption, scattering, transmittance and reflectance. The MC method utilizes stochastic models in which the expected value of random variables (determined by optical properties) to simulate these events. The expected value is estimated by averaging the behavior of many independently simulated photons (or photon packets). Due to its statistical nature, use of MC in computing the forward model in DOT and DFT requires a large number of photons to obtain a statistically meaningful result, which is in general computationally time-consuming even on modern computers with hardware acceleration. Each photon’s trajectory is governed
by four key optical properties, which are absorption coefficient ($\mu_a$), scattering coefficient ($\mu_s$), anisotropy ($g$) and refractive index ($n$). The “phase function” is also critical in modeling photon behavior. Specifically, $\mu_a$ determines how far a photon can propagate before it is absorbed; $\mu_s$ determines the mean length of each random walk; $g$ or the phase function determines the next random walk direction; $n$ determines if reflectance or transmittance happens at a boundary with mis-matched optical properties according to Fresnel’s laws.

### 2.2.2 Mesh-base Monte Carlo Introduction

Several researcher groups have been working on the MC method for modeling light propagation in diffusive tissue since the early 1980s, and many freely provide their MC software online. The Monte-Carlo Multi-Layer (MCML) codebase was originally developed by Wang and can solve layered media with different optical properties in cylindrical or slab geometries[26]. Boas et al. developed a tMCimg which can model photon migration in more complex and heterogeneous geometry structures with irregular boundaries as is frequently encountered in experimental DOT and DFT imaging [10]. Chen’s time-gated perturbation MC code is suitable for functional DOT in preclinical scenarios[15]. In our research we have used Mesh-based Monte Carlo (MMC), an open source software developed by Fang, which is used to model photon propagation. MMC is an MC software package which supports time-resolved light propagation and simulates photon migration in volumetric mesh by multiple-thread computing.

MMC has advantage in speed and modeling complex geometry over other MC softwares. MMC exploits Single Instruction Multiple Data (SIMD) based computation and branch-less design to accelerate ray-tetrahedron intersection tests and yield a 2-fold speed-up for ray-tracing calculations on a multi-core CPU.[28]. Parallel computing significantly accelerates the speed of MC simulation. Also, MMC increases the accuracy of modeling curved boundaries and the efficiency of simulation. Traditional MC methods are
usually voxel-based which require more memory and computation to model curved boundary by decreasing the size of each grid. Mesh is also helpful to model complex and curved boundary geometry, such as mice, for further research in our group. Figure 2.3 shows an example of finite element mesh modeling a rat head. With the advantages mentioned above, MMC ran rapidly for our studies on a Unix workstation with 40 Intel XeonE7-4850 CPUs at 2.00GHz.

To generate a forward model by MMC, a geometry structure first needs to be converted to a tetrahedral mesh. The toolbox used to mesh a structure in our research is iso2mesh\textsuperscript{[29]}. A meshed structure is shown in the Figure 2.3.

\textbf{Figure 2.3:} A finite element mesh for a mouse hat with 3949 nodes and 20410 elements

Next, parameters are defined including optical properties, source positions, detector positions and so forth., by a configuration file. Figure 2.4 shows an example of a configuration file.
Diffusion theory models photon propagation in semi-infinite 2-D slab, while MMC simulates photon propagation in a 3-D space. It is necessary to reduce 3-D MMC sensitivity matrix to 2-D by selecting a plain intersecting sources and detectors positions in MMC 3-D geometry model.

2.2.3 Monte Carlo Method 1 - Adjoint Method

In the MC-Adj, detectors are considered to behave in the same way as sources in the reverse direction. Therefore, the behavior of photon packets are simulated separately from both source side and detector side, so that the fluence distributions of source side and detector side can both be obtained. From the Equation 2.6 and Equation 2.8, \( U_0(\vec{r}, \vec{r}_s) \) or \( U_0(\vec{r}, \vec{r}_s, t) \) is obtained by the simulations from source side, and similarly, simulations from detector side provide \( G(\vec{r}_d, \vec{r}) \) or \( G(\vec{r}_d, \vec{r}, t) \). In this case, the weight matrix is calculated with the equations above. In principle, the MC method yields more accurate modeling of light propagation than diffusion theory, since it is considered a direct implementation of the RTE and since boundaries are explicitly modeled. Using time-resolved supported MC software (such as MMC), it is also possible to model the forward problem in both continuous-wave and time-resolved mode. Figure 2.5 shows the procedure to create the weight matrix using the MC-Adj:
2.2.4 Monte Carlo Method 2 - Photon Tracking

MC-PT provides a method to model the forward problem between source-detector pairs with simulations originating from the source position only. In the MC-PT simulation, a number of photon packets are launched in the diffusive media, and some photons are “captured” at pre-defined detector positions at specific times. Following the MC approach, if the photon reaches \( r \) at time \( t_{s,r} \), the weight of the \( i_{th} \) photon \( w_i \) at \( r \) has decreased to:

\[
  w_i(r_s, r, t_{s,r}) = w_{i,0} \exp\left(- \sum_{j=1}^{p_i} \mu_a(r_j) l(r_j) \right)
\]

(2.9)

where, \( w_{i,0} \) is the initial weight of this photon, \( r_j (j = 1, ..., p_i) \) are the sub-regions that the photon consequently passes through from \( r_s \) to \( r \), and \( l_i(r_j) \) is the path length that the photon passes at \( r_j \).

Similarly in MC-PT, the weight \( w'_i(r_s, r_d, r, t_{s,r}) \) at position \( r \) can be calculated as:

\[
  w'_i(r_s, r_d, r, t_{s,r}) = w_i(r_s, r_d, t_{s,d}) \exp\left(- \sum_{j=1}^{p_i} \delta \mu'_a(r_j) l(r_j) \right)
\]

(2.10)

where \( w_i(r_s, r_d, t_{s,d}) \) is the exit weight at time \( t_{s,d}[30] [31] \).

Since computer programs generate a pseudo-random number sequence which is selected by a seed at the
beginning a simulation, MC-PT can be executed in two steps. First, a full simulation with a large number of photons is launched in the media. A seed of the random number generator is initialized for every new photon. If the photon hits the detectors, the corresponding seed is called “successful” and saved to memory. In the second step, the “successful” photons with the seeds are launch again in the same media. The “successful” photons repeat the same path in the previous full simulation. In the way, we can obtain photon propagation path in a diffusive medium[30]. This is significantly less memory intensive (and computes significantly more quickly) than attempting to store photon paths during the initial full simulation.

However, MC-PT is more computationally expensive than MC-Adj, because in highly diffusive media with pathlengths on the orders of cm, the vast majority of photons are not captured by detectors (particularly when considering specific detection time windows). Therefore, in order to generate a statically stable forward model, very large numbers of photons need to be launched in the initial simulation. In our simulations, we used $2^{31}$ launched photons to generate meaningful data at very early time points. Figure 2.6 shows weight matrice in a semi-infinite slab with 2cm thickness by MC-PT. MC-Adj models photon propagation by simulating from both source side and detector side, so it does not model real photon flying paths in the diffusive medium, which may cause inaccuracy. MC-PT detectors accept photons from directions within a numerical aperture, whereas MC-Adj models detectors in the same way as sources with a pulse light with one direction. In small geometry with sizes of a couple photon mean free paths($\frac{1}{D} \approx 0.06mm$), sensitivity matrix near a detector is more like a pencil-beam light shoots into diffusive medium other than a smooth photon path accepted by detectors.
2.3 Description of Geometry and Optical Property

In this section, the geometries we studied for diffusion theory forward model, adjoint MC and MC-PT methods are described. In the DFT and DOT literature, the two most commonly modeled geometries are semi-infinite slab (for planar instruments) and cylinder (for radially-symmetrical instruments). These are described here for different sizes, source-detector geometries and optical properties as follows.

2.3.1 Semi-infinite Slab Geometries

We first studied a semi-infinite slab model, since this is frequently used to model DOT and DFT in planar geometry instruments [32] [33]. For these, we compared transmittance sensitivity matrices of diffusion theory, MC-Adj and MC-PT in semi-infinite slabs with thickness of 2cm, 1cm, 5mm and 3mm. The sizes are chosen because our team is performing ongoing imaging work at these physical scales [24] [34]. For example, small animals, such as mice, which we used in DFT are about 2cm thick [35] [36], and limbs of mice in DFFC are about 3mm thick [34].

In order to make slabs semi-infinite with the MC methods, we created long and wide enough slabs with the desired thickness so that the boundary condition be ignored. For example, the 2cm thick slab has...
12cm length and 12cm width, since statistically a negligible fraction of launched photons will travel to that distance from the source position.

Furthermore, the positions of detectors were varied along the media surface for investigating situations when sources and detectors are not directly opposite each other. This happens in most DFT and DOT instruments as shown in the Figure 1.1 [24]. Figure 2.7 visualizes the slab model described above:

![Figure 2.7: Photons are simulated in the slab with large enough length and width, then the fluence distributions in the light blue plain are taken out for comparison](image)

For the comparisons of time-resolved forward models, the time is considered differently upon the characters of each method. DT is able to calculate forward model at any time by involving the time parameter in the formula. Time-resolved MC-Adj depends on the time gates defined in MMC configuration files. For the 2cm and 1cm thick slab, the time step used was 10ps, because the temporal point spread function (TPSF) of large geometry changes slow along time, and 10ps does not make significant differences between two time points. Since the photon propagation time is relatively long in highly scattered media, large time steps are more computationally efficient. For the 5mm and 3mm slab, the time step used was 2ps, because the TPSF changes more rapidly in small geometries.

In the time-resolved MC-PT, the random number seeds of photons that arrive at each detector in timebins
must be saved. For example, a forward model at time $T$ is calculated by replaying photons that arrived in the time range $[T-t, T+t]$. In order to replay enough detected photons for a useful forward model as well as have good time resolution for TPSF, sizes of timebins are different according to the thicknesses of slabs. Table 2.1 shows the details about timebin sizes. The time resolutions are treated similarly in the other geometry structures in the following sections.

<table>
<thead>
<tr>
<th>Slab Thickness</th>
<th>Timebin Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2cm slab</td>
<td>[T-20ps, T+20ps]</td>
</tr>
<tr>
<td>1cm slab</td>
<td>[T-10ps, T+10ps]</td>
</tr>
<tr>
<td>5mm slab</td>
<td>[T-4ps, T+4ps]</td>
</tr>
<tr>
<td>3mm slab</td>
<td>[T-2ps, T+2ps]</td>
</tr>
</tbody>
</table>

### 2.3.2 Cylindrical Geometries

Cylinder models were considered to be more complex geometries, because there are more boundary effects than slabs. Four different sizes of cylinders were modeled, which were 2cm diameter, 1cm diameter, 5mm diameter and 3mm diameter. The lengths of the four cylinder types were 10cm in all cases, which was long enough compared to the diameters so that they boundary effects were negligible. Detectors were placed at four positions as in Figure 2.8: directly opposite to the source, and 45 degrees, 90 degrees and 135 degrees opposite to the source. The width of the time bins used here for time-resolved sensitivity matrices were the same as those in the slab models.

### 2.3.3 Irregular Geometries

Even though Cylinder models have more boundary condition than slab models, we still want to investigate how the three forward model methods perform with more boundary effects. Therefore, we created a model
Figure 2.8: The placements of detectors in cylindrical geometry.

as in Figure 2.9.

Figure 2.9: Irregular geometry shape, size and detector placements.
2.3.4 Optical Properties

In the all the models (slabs with offsets, cylinders with offsets and irregular geometry), we have the same optical properties, which are $\mu_a = 0.015/mm$, $\mu_s = 11.33/mm$, $g = 0.85$, $n = 1.37$, this set of optical properties is chosen because they are close to the optical properties in biological tissues that we are interested in imaging. Also, our team’s previous work is based on this set of optical properties [24] [20]. In order to compare the three methods with different optical properties, we also calculated forward models with half and double the optical properties ($[\mu_a = 0.0075/mm, \mu_s = 5.665/mm, g = 0.85, n = 1.37]$ and $[\mu_a = 0.03/mm, \mu_s = 22.67/mm, g = 0.85, n = 1.37]$, respectively) in 2cm slab with 0cm, 1cm and 2cm offset.

2.4 Metrics for Comparison of Forward Models

In order to quantify the agreement or disagreement between sensitivity matrices computed with different methods, it was necessary to select specific metrics for comparison. We chose these as follows:

1. Full Width of Half Maximum (FWHM): FWHM presents how far photons spread in diffusive medium with different forward models. We calculate FWHM at the central of the slab, 1mm to detectors and 1mm to sources. Figure 2.10 shows how we calculate FWHM.

2. Contour: Contour indicates the fluence distributed in the diffusive medium with the same value. Therefore, the contour is a good method to compare the differences between different forward models. For slab model, we plot contours with the mean value at the central line in the slab medium. While for cylinder model, the value we chose is the value at middle point between source and detector. Some MC software
authors, for example Fang\cite{19} \cite{28} and Sassaroli\cite{30}, also use contour to validate their MC simulations. The contour in the middle of Figure 2.11 is that two contours of MC-Adj and MC-PT forward model are plotted together such that we can compare them directly.

3. Contour Area: A contour encloses one or multiple regions in the diffusive medium. The area of the fields enclosed by contours is a method to tell the differences among forward models as well. The two contours on the left of Figure 2.11 are MC-Adj and MC-PT contours plotted separately, such that the areas can be calculated by enclosed curves for MC-Adj and MC-PT.

4. Overlap: In the contours with different forward models, some parts of contour are overlapped while some are not. We involve $\text{overlap} = \frac{A_{\text{contour}} \cap B_{\text{contour}}}{A_{\text{contour}} \cup B_{\text{contour}}}$ as a metric in this research.
The contour on the right of Figure 2.11 is still the contour of MC-Adj and MC-PT, but the outer curves are marked as blue and the inner curves as black, such that we can get overlap by calculating area of outer curves and inner curves, respectively. The overlap is calculated by $\text{overlap} = \frac{\text{Area}_{\text{innercurve}}}{\text{Area}_{\text{outercurve}}}$.

**Figure 2.11:** (left column) MC-Adj and MC-PT contours plotted separately, such that the areas can be calculated by enclosed curves for MC-Adj and MC-PT. (middle column) two contours of MC-Adj and MC-PT forward model are plotted together. (right column) The outer and inner contours are marked with blue and black, respectively, such that the overlap is calculated by $\text{overlap} = \frac{\text{Area}_{\text{innercurve}}}{\text{Area}_{\text{outercurve}}}$.

5. Deviation: To more quantitatively analyze these data, we computed the deviation between the DT and MC-Adj and between the MC-Adj and MC-PT methods, respectively. As such the MC-Adj method was implicitly used as a reference method, because it is assumed to have medium accuracy and computation cost compared with the other two methods and used frequently in the literature\^[37]. Specifically, deviations were calculated by the following formulae:
\[
Deviation = \frac{|\text{Metrics}_{DT} - \text{Metrics}_{MC-Adj}|}{\text{Metrics}_{MC-Adj}} \tag{2.11}
\]

\[
Deviation = \frac{|\text{Metrics}_{MC-PT} - \text{Metrics}_{MC-Adj}|}{\text{Metrics}_{MC-Adj}} \tag{2.12}
\]

To further quantify our analysis, we specified that two methods were not in agreement for a given scenario (geometry, size, timepoint etc.) if the deviation between them is greater than 10%. While this 10% threshold is somewhat arbitrary, we determined by thoroughly reviewing our data sets that it is useful in identifying scenarios with significant disagreement.
Chapter 3

Results

In this chapter, we present the results of our computations of sensitivity matrices using the three methods described earlier in this thesis, i.e. Diffusion theory, MC Adjoint and MC Photon Tracking. Results computed for a number of representative scenarios will be presented including cylindrical and slab geometries with sizes ranging from 3 to 20 mm (thickness or diameter). The relative agreement between the three methods will be presented with respect to the metrics defined in Chapter 2. Implications of these results for our DOT and DFT studies will be discussed in Chapter 4.

3.1 Slab Geometries

3.1.1 Time-resolved forward model

The results of the sensitivity function calculations for each of the 3 computation methods are shown in Figure 3.1; here, the output of all three are shown on the same figure for clarity. For these the, i) temporal point spread function observed at the detector, ii) FWHM of the sensitivity function in the middle of the diffusive medium, iii) FWHM of the sensitivity function close to (1 mm from) the detector,
iv) FWHM of the sensitivity function close to (1 mm from) the source, and v) the contour area are shown. Representative “large slab” geometries are shown for either 1 or 2 cm thickness, with either 0 or 1 cm source-detector offsets. The continuous wave (continuous intensity) results are shown by the horizontal lines in each pane. By inspection, the TPSFs (Figure 3.1, row 1) are almost identical for the three forward models. This is somewhat expected, since diffusion theory is generally accepted to be accurate for relatively large tissue volumes, away from boundaries or sources. When comparing the sensitivity function FWHMs (Figure 3.1, row 2) some differences at early time points following the laser pulse were observed. Moreover, slightly greater disagreements were observed between the DT and MC-Adj and MC-PT sensitivity functions for cases with larger source-detector offsets. The contour areas have differences at late time sensitivity matrices, specifically with respect to DT and the MC methods. The most significant differences were observed for the sensitivity function FWHM measurements close to (1mm from) the detector. The observed differences are due to a number of reasons. First, as noted in Chapter 2 the diffusion theory forward models are derived with the implicit assumption that sources and detectors are isotropic, so that the FWHM continues to increase with time. This disagreement is again unexpected, since DT is understood to be inaccurate close to boundaries and light sources. For the MC-Adj method the detectors are assumed to be infinitely small point detectors (sources), so that the sensitivity FWHM close to the detector is narrower than the MC-PT case, where a finite detector size of 1 mm was modeled. This disagreement, while predictable, is relevant for experimental measurements where detectors have finite sizes.

3.1.1.1 TPSF Analysis

To start with the comparisons in slab model, we first present points in TPSF corresponding to the absolute time (i.e. 10% in TPSF rising edge of peak is at 330ps in 2cm slab with 0cm offset). More TPSF time points can be found in the following Table 3.1, Table 3.2, Table 3.3 and Table 3.4. Also, these tables can
Figure 3.1: Results in the large slab model are presented in this figure. Metrics are plotted as a function of time. The dash lines in the middle FWHM, 1mm to detector FWHM, 1mm to source FWHM and Contour Area are values in CW mode.
Figure 3.2: Results in the small slab model are presented in this figure. Metrics are plotted as a function of time. The dash lines in the middle FWHM, 1mm to detector FWHM, 1mm to source FWHM and Contour Area are values in CW mode.
be used as reference for points at TPSF corresponding to absolute time in further sections.

### Table 3.1: TPSF Point in 2cm Slab

<table>
<thead>
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<th>Methods</th>
<th>1% rising</th>
<th>5% rising</th>
<th>10% rising</th>
<th>50% rising</th>
<th>100%</th>
<th>50% falling</th>
</tr>
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### Table 3.2: TPSF Point in 1cm Slab

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### Table 3.3: TPSF Point in 5mm Slab

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<td>MC-Adj</td>
<td>36ps</td>
<td>42ps</td>
<td>46ps</td>
<td>64ps</td>
<td>104ps</td>
<td>188ps</td>
</tr>
<tr>
<td></td>
<td>MC-PT</td>
<td>40ps</td>
<td>44ps</td>
<td>48ps</td>
<td>64ps</td>
<td>110ps</td>
<td>186ps</td>
</tr>
</tbody>
</table>
### Table 3.4: TPSF Point in 3mm Slab

<table>
<thead>
<tr>
<th>Offsets</th>
<th>Methods</th>
<th>1% rising</th>
<th>5% rising</th>
<th>10% rising</th>
<th>50% rising</th>
<th>100%</th>
<th>50% falling</th>
</tr>
</thead>
<tbody>
<tr>
<td>0cm offset</td>
<td>DT</td>
<td>4.3ps</td>
<td>6ps</td>
<td>6.62ps</td>
<td>10.5ps</td>
<td>20ps</td>
<td>41ps</td>
</tr>
<tr>
<td></td>
<td>MC-Adj</td>
<td>6.48ps</td>
<td>8.33ps</td>
<td>9.38ps</td>
<td>13.6ps</td>
<td>22ps</td>
<td>52ps</td>
</tr>
<tr>
<td></td>
<td>MC-PT</td>
<td>12ps</td>
<td>12.34ps</td>
<td>12.68ps</td>
<td>14.8ps</td>
<td>18ps</td>
<td>46ps</td>
</tr>
<tr>
<td>0.15cm offset</td>
<td>DT</td>
<td>6ps</td>
<td>7.5ps</td>
<td>8.5ps</td>
<td>13ps</td>
<td>24ps</td>
<td>50.5ps</td>
</tr>
<tr>
<td></td>
<td>MC-Adj</td>
<td>14ps</td>
<td>14.5ps</td>
<td>15.18ps</td>
<td>19.25ps</td>
<td>26ps</td>
<td>56ps</td>
</tr>
<tr>
<td></td>
<td>MC-PT</td>
<td>14ps</td>
<td>14.3ps</td>
<td>14.7ps</td>
<td>18ps</td>
<td>26ps</td>
<td>54ps</td>
</tr>
<tr>
<td>0.3cm offset</td>
<td>DT</td>
<td>9.6ps</td>
<td>12ps</td>
<td>13.6ps</td>
<td>20.6ps</td>
<td>37.4ps</td>
<td>78.2ps</td>
</tr>
<tr>
<td></td>
<td>MC-Adj</td>
<td>19ps</td>
<td>22ps</td>
<td>23ps</td>
<td>28ps</td>
<td>42ps</td>
<td>80ps</td>
</tr>
<tr>
<td></td>
<td>MC-PT</td>
<td>18.42ps</td>
<td>20.14ps</td>
<td>22ps</td>
<td>26ps</td>
<td>38ps</td>
<td>78ps</td>
</tr>
</tbody>
</table>

From the time points listed in the tables, the two MC methods have good agreements with respect to time. However, the DT TPSF predicts photon arrival at the detector slightly ($\approx 10\text{ps}$) earlier than the MC TPSF. Because MC-Adj and MC-PT agree with each other, we simply use MC-Adj TPSF to compare with DT TPSF. Deviation of time points at 10% rising and peak are calculated in the following Table 3.5. Time points do not have significant differences in large size slabs, while the agreements become worse when the size is decreasing. The deviation is up to 44.01% in the 3mm slab with 0.15cm offset. This results about TPSF are actually as our expected. For example, Alfano’s research has similar conclusion that TPSF agrees better in large geometry than in small geometry [27]. Furthermore, we should notice that DT is not valid to model photon propagation at very early times. For example, in the 5mm slab with 0cm offset geometry the 10% time is 18ps, however the ballistic time for 5mm slab is 22ps, so the DT forward model is not physically meaningful in that case. Also, there remains a challenge to calculate forward model at very early time in small geometry.

#### 3.1.1.2 Large Slab Geometries: Diffusion Theory vs the MC-Adjoint Method

As shown in table 3.6 and 3.7, the results from DT and MC-Adj methods agreed well with each other with respect to the sensitivity function FWHM in the center of the media and contour area under nearly all
Table 3.5: Time Point Deviation (DT vs MC-Adj)

<table>
<thead>
<tr>
<th>slab size</th>
<th>Offsets</th>
<th>10% rising</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2cm slab</td>
<td>0cm offset</td>
<td>7.69%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>1cm offset</td>
<td>9.68%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>2cm offset</td>
<td>4.55%</td>
<td>0%</td>
</tr>
<tr>
<td>1cm slab</td>
<td>0cm offset</td>
<td>15.66%</td>
<td>10.53%</td>
</tr>
<tr>
<td></td>
<td>0.5cm offset</td>
<td>10.53%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>1cm offset</td>
<td>11.19%</td>
<td>0%</td>
</tr>
<tr>
<td>5mm slab</td>
<td>0cm offset</td>
<td>28.00%</td>
<td>15.15%</td>
</tr>
<tr>
<td></td>
<td>0.25cm offset</td>
<td>23.61%</td>
<td>16.67%</td>
</tr>
<tr>
<td></td>
<td>0.5cm offset</td>
<td>19.57%</td>
<td>9.62%</td>
</tr>
<tr>
<td>3mm slab</td>
<td>0cm offset</td>
<td>29.42%</td>
<td>9.09%</td>
</tr>
<tr>
<td></td>
<td>0.15cm offset</td>
<td>44.01%</td>
<td>7.69%</td>
</tr>
<tr>
<td></td>
<td>0.3cm offset</td>
<td>40.87%</td>
<td>10.95%</td>
</tr>
</tbody>
</table>

Circumstances. Exceptions include for very early time (90ps, 20% rising edge) in the 1cm slab geometry with 0cm offset. However, as detailed in the table, the contour areas showed more variability, although again at very early or very late times.

Table 3.6: 2cm Slab Agreement Time Table (DT vs MC-Adj)

<table>
<thead>
<tr>
<th>metrics</th>
<th>0cm offset</th>
<th>1cm offset</th>
<th>2cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWHM</td>
<td>anytime</td>
<td>anytime</td>
<td>anytime</td>
</tr>
<tr>
<td>AREA</td>
<td>[start time, 1130ps]</td>
<td>[start time, 1220ps]</td>
<td>[start time, 1260ps]</td>
</tr>
</tbody>
</table>

Table 3.7: 1cm Slab Agreement Time Table (DT vs MC-Adj)

<table>
<thead>
<tr>
<th>metrics</th>
<th>0cm offset</th>
<th>0.5cm offset</th>
<th>1cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWHM</td>
<td>[90ps,end time]</td>
<td>anytime</td>
<td>anytime</td>
</tr>
<tr>
<td>AREA</td>
<td>[70ps,470ps]</td>
<td>[80ps,530ps]</td>
<td>[start,540ps]</td>
</tr>
</tbody>
</table>

3.1.1.3 Small Slab Geometries: Diffusion Theory vs the MC-Adjoint Method

In general, for small slab geometries (3 mm and 5 mm thicknesses) the DT and MC-Adj methods agreed well except for on the rising edge in small geometries (about 50% rising edge of TPSF). As indicated, results from these two methods showed greater disagreement for small than larger geometries at early
times. Specially, greater than 10% deviation was observed for the sensitivity function FWHM calculations at times earlier than 50% of peak on the rising edge of the TPSF curve, and at times earlier than 10% of the peak for contour area deviations. Although this is significant for specific situations, (i.e. at very early times in small geometries), in sensitivity functions computed with DT and MC-Adj methods showed very good agreement in general.

| Table 3.8: 5mm Slab Deviation Table (DT vs MC-Adj) |
|----------------------------------|--|--|--|
| metrics | 0cm offset | 0.25cm offset | 0.5cm offset |
| FWHM | [40ps, end] | [44ps, end] | [50ps, end] |
| AREA | [48ps, end] | [52ps, end] | [60ps, end] |

| Table 3.9: 3mm Slab Deviation Table (DT vs MC-Adj) |
|----------------------------------|--|--|--|
| metrics | 0cm offset | 0.15cm offset | 0.3cm offset |
| FWHM | [24ps, end] | [24ps, end] | [26ps, end] |
| AREA | [32ps, end] | [34ps, end] | [38ps, end] |

3.1.1.4 Slab Geometries: MC Adjoint vs. MC Photon Tracking Methods

Generally, MC-Adj and MC-PT have excellent agreement at most situations, however measured differences in sensitivity functions were observed only at very early time points on the rising edge of the TPSF curves. In Figure 3.3, MC-Adj created an unreasonable weight matrix at 120ps. Because both photons from sources and detectors are not able to reach the other side, but they have weight in the middle of medium, forward models with fluence in the middle but at source and detector side are generated.

The measured differences may be caused by two factors. First, the MC-PT forward model may be not accurate due to limited number of photons captured at very early time. Though in our research we used a very large number of photons \(2^{31}\), as we can see from the Table 3.11, less than 100 photons are detected at very early time (170ps). In order to elaborate how many photons are enough, it is necessary to compare
forward models with replaying different numbers of photons by MC-PT. In Figure 3.4, the first column is the forward model at 230ps in the 2cm slab with 1cm offset when about 100 photons are captured. The middle line profile is not so smooth especially at the right half profile. The second column is the the forward model at 290ps in 2cm slab with 1cm offset when about 1000 photons are detected. The profile in 1000 photons Jacobian is smoother than the profile in 100 photons Jacobian, however noise points still exist but do not affect much on FWHM. The last column is the forward model in the same geometry with about 10000 photons. The profile is relatively smooth and we believe that FWHM calculated from it is stable. All in all, noisy profiles may occur when hundreds of photons are replayed. While, forward models generated by thousands of photons are meaningful.

For the second factor, if we get enough photons to model photon propagations by MC-PT, measured differences are caused by different modeling methods between MC-Adj and MC-PT. In large slabs (refers to Table 3.10 - Table 3.13), before deviation is greater than 10%, only hundreds of photon are detected, so it is unfair to say MC-Adj is inaccurate under these circumstances, and it is prohibitively expensive to model
Figure 3.4: The three forward models are for 2cm slab with 1cm offset. The left-most column is the forward model at 230ps with replaying about 100 photons. The middle column is the forward model at 290ps with replaying about 1000 photons. The right-most column is the forward model at 410ps with replaying about 10000 photons.

photon propagation by MC-PT. However, in small geometry (refers to Table 3.14 - Table 3.17), before the inaccurate time (deviation > 10%), MC-PT can obtain more than thousands of photons captured by detectors. In these case, as expected, the detectors modeled by infinite impulse light reduce accuracies in MC-Adj. MC-PT is more accurate at early time as long as detectors can accept enough photons (thousands of photons), but it is still an open question that which method is more accurate at early time when not enough photons accept.

Table 3.10: 2cm Slab Agreement Time Table (MC-Adj vs MC-PT)

<table>
<thead>
<tr>
<th>metrics</th>
<th>0cm offset</th>
<th>1cm offset</th>
<th>2cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWHM</td>
<td>240ps, end</td>
<td>260ps, end</td>
<td>540ps, end</td>
</tr>
<tr>
<td>AREA</td>
<td>anytime</td>
<td>270ps, end</td>
<td>380ps, end</td>
</tr>
</tbody>
</table>
### Table 3.11: Numbers of Photo Captured in 2cm Slab around Deviated Time

<table>
<thead>
<tr>
<th>offsets</th>
<th>time1 : photons</th>
<th>time2 : photons</th>
<th>time3 : photons</th>
<th>time4 : photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>0cm offset</td>
<td>170ps : 47</td>
<td>190ps : 216</td>
<td>210ps : 654</td>
<td>230ps : 1554</td>
</tr>
<tr>
<td>1cm offset</td>
<td>210ps : 35</td>
<td>230ps : 110</td>
<td>250ps : 262</td>
<td>270ps : 553</td>
</tr>
<tr>
<td>2cm offset</td>
<td>490ps : 522</td>
<td>510ps : 669</td>
<td>530ps : 876</td>
<td>550ps : 1050</td>
</tr>
</tbody>
</table>

### Table 3.12: 1cm Slab Agreement Time Table (MC-Adj vs MC-PT)

<table>
<thead>
<tr>
<th>metrics</th>
<th>0cm offset</th>
<th>0.5cm offset</th>
<th>1cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWHM</td>
<td>[90ps, end]</td>
<td>anytime</td>
<td>[130ps, end]</td>
</tr>
<tr>
<td>AREA</td>
<td>[70ps, end]</td>
<td>[70ps, end]</td>
<td>anytime</td>
</tr>
</tbody>
</table>

### Table 3.13: Numbers of Photo Captured in 1cm Slab around Deviated Time

<table>
<thead>
<tr>
<th>offsets</th>
<th>time1 : photons</th>
<th>time2 : photons</th>
<th>time3 : photons</th>
<th>time4 : photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>0cm offset</td>
<td>50ps : 61</td>
<td>70ps : 7961</td>
<td>90ps : 45791</td>
<td>110ps : 105937</td>
</tr>
<tr>
<td>0.5cm offset</td>
<td>50ps : 1</td>
<td>70ps : 533</td>
<td>90ps : 6657</td>
<td>110ps : 24611</td>
</tr>
<tr>
<td>1cm offset</td>
<td>90ps : 11</td>
<td>110ps : 235</td>
<td>130ps : 1252</td>
<td>150ps : 3446</td>
</tr>
</tbody>
</table>

### Table 3.14: 5mm Slab Agreement Time Table (MC-Adj vs MC-PT)

<table>
<thead>
<tr>
<th>metrics</th>
<th>0cm offset</th>
<th>0.25cm offset</th>
<th>0.5cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWHM</td>
<td>[30ps, end]</td>
<td>[36ps, end]</td>
<td>[42ps, end]</td>
</tr>
<tr>
<td>AREA</td>
<td>[30ps, end]</td>
<td>[36ps, end]</td>
<td>[40ps, end]</td>
</tr>
</tbody>
</table>

### Table 3.15: Numbers of Photo Captured in 5mm Slab around Deviated Time

<table>
<thead>
<tr>
<th>offsets</th>
<th>time1 : photons</th>
<th>time2 : photons</th>
<th>time3 : photons</th>
<th>time4 : photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>0cm offset</td>
<td>24ps : 25039</td>
<td>28ps : 123278</td>
<td>32ps : 256884</td>
<td>36ps : 359148</td>
</tr>
<tr>
<td>0.25cm offset</td>
<td>28ps : 8111</td>
<td>32ps : 39028</td>
<td>36ps : 87908</td>
<td>40ps : 136558</td>
</tr>
<tr>
<td>0.5cm offset</td>
<td>32ps : 5</td>
<td>36ps : 240 photons</td>
<td>40ps : 1671</td>
<td>44ps : 5205</td>
</tr>
</tbody>
</table>

### Table 3.16: 3mm Slab Agreement Time Table (MC-Adj vs MC-PT)

<table>
<thead>
<tr>
<th>metrics</th>
<th>0cm offset</th>
<th>0.15cm offset</th>
<th>0.3cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>FWHM</td>
<td>[14ps, end]</td>
<td>[16ps, end]</td>
<td>[24ps, end]</td>
</tr>
<tr>
<td>AREA</td>
<td>[16ps, end]</td>
<td>anytime</td>
<td>[22ps, end]</td>
</tr>
</tbody>
</table>

### Table 3.17: Numbers of Photo Captured in 3mm Slab around Deviated Time

<table>
<thead>
<tr>
<th>offsets</th>
<th>time1 : photons</th>
<th>time2 : photons</th>
<th>time3 : photons</th>
<th>time4 : photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>0cm offset</td>
<td>12ps : 552</td>
<td>14ps : 35480</td>
<td>16ps : 929894</td>
<td>18ps : 1105383</td>
</tr>
<tr>
<td>0.15cm offset</td>
<td>14ps : 2548</td>
<td>16ps : 91251</td>
<td>18ps : 278790</td>
<td>20ps : 413303</td>
</tr>
<tr>
<td>0.3cm offset</td>
<td>20ps : 1841</td>
<td>22ps : 12328</td>
<td>24ps : 33730</td>
<td>26ps : 57803</td>
</tr>
</tbody>
</table>
3.1.2 Continuous Wave Sensitivity Functions

The results for sensitivity functions computed for continuous wave (time-integrated) scenarios are shown in Tables 3.18-3.21 respectively. Generally speaking the sensitivity functions computed with both the MC-Adj and MC-PT methods agreed very well in nearly all situations. The largest deviation observed was about 6% for the very small 3 mm slab geometry with a large, 0.15 cm offset. Likewise, deviations for the sensitivity function FWHM in the middle of the media between DT and MC-Adj were less than 10% except for the specific case of the 3mm thickness slab with 0 cm detector offset. The contour areas exhibited greater deviation, but still were generally under (or close to) 10%. The largest deviation observed was 12.23% for the 5mm slab thickness with 0cm offset. As such, surprisingly good agreement was observed for DT for all the geometries tested, despite the large number of simplifying assumptions (e.g. ignoring boundary conditions). These data generally disagree with previously published assertions that DT is inappropriate for modeling photon propagation in small animal geometries [13] even in the continuous wave case.

<table>
<thead>
<tr>
<th>Table 3.18: 2cm Slab Deviation in CW Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>methods</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Diffusion theory vs Adjoint method</td>
</tr>
<tr>
<td>Diffusion theory vs Adjoint method</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3.19: 1cm Slab Deviation in CW Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>methods</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Diffusion theory vs Adjoint method</td>
</tr>
<tr>
<td>Diffusion theory vs Adjoint method</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
</tr>
</tbody>
</table>
Table 3.20: 5mm Slab Deviation in CW Table

<table>
<thead>
<tr>
<th>methods</th>
<th>metrics</th>
<th>0cm offset</th>
<th>0.25cm offset</th>
<th>0.5cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion theory vs Adjoint method</td>
<td>FWHM</td>
<td>7.94%</td>
<td>0.76%</td>
<td>1.20%</td>
</tr>
<tr>
<td>Diffusion theory vs Adjoint method</td>
<td>AREA</td>
<td>12.23%</td>
<td>10.56%</td>
<td>10.43%</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
<td>FWHM</td>
<td>3.7%</td>
<td>0.09%</td>
<td>1.00%</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
<td>AREA</td>
<td>2.56%</td>
<td>1.50%</td>
<td>0.55%</td>
</tr>
</tbody>
</table>

Table 3.21: 3mm Slab Deviation in CW Table

<table>
<thead>
<tr>
<th>methods</th>
<th>metrics</th>
<th>0cm offset</th>
<th>0.15cm offset</th>
<th>0.3cm offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion theory vs Adjoint method</td>
<td>FWHM</td>
<td>11.44%</td>
<td>1.23%</td>
<td>4.90%</td>
</tr>
<tr>
<td>Diffusion theory vs Adjoint method</td>
<td>AREA</td>
<td>12.13%</td>
<td>10.21%</td>
<td>8.95%</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
<td>FWHM</td>
<td>0.89%</td>
<td>6.14%</td>
<td>5.19%</td>
</tr>
<tr>
<td>Adjoint method vs Photon tracking</td>
<td>AREA</td>
<td>1.72%</td>
<td>0.30%</td>
<td>0.92%</td>
</tr>
</tbody>
</table>

3.2 Cylindrical Geometries

In this section, the results from sensitivity functions in cylindrical models will be presented to show how the three methods perform in this geometry. As discussed in Chapter 2, these will be compared by percentage of overlap of the contour area. Similarly with the slab model, DT vs the MC-Adj and the MC-Adj vs. the MC-PT methods will be discussed separately. Figure 3.5 and Figure 3.6 are contours in cylinders with 2cm, 1cm, 5mm, 3mm diameter with different detector placements. In the cylindrical geometries, we also run an isotopic MC-Adj in which detectors are modeled as an isotropic light source other than the pencil-beam MC-Adj detector. However, the differences between isotropic MC-Adj and normal MC-Adj are not significant, so in the discussion normal MC-Adj is used to compare with DT and MC-PT. In the future work, we will investigate differences between isotropic MC-Adj and normal MC-Adj.

3.2.1 Cylindrical Geometries: Diffusion Theory vs the MC Adjoint Method

As shown in Figure 3.5 and Figure 3.6, in general the percentage overlap of the contour area decreased with increasing detector angle (see Figure 2.8 for definition of detector geometries). In the case of 0 degree
Chapter 3. Result

Figure 3.5: the contours of DT, MC-Adj, MC-PT forward model plotted in large size cylinders with different detector placement and time points at TPSF in the same scenario. Red contours are MC-PT; blue contours are normal MC-Adj; cyan contours are isotropic MC-Adj (it is almost the same with normal MC-Adj); black contours are DT. The number in the legend is the area enclosed by contours corresponding to each method.

detector offset (i.e. source and detector directly opposite each other), the overlap agreements are in the range of 80% to 90%. With increasing angle of detector positioning this decreases significantly; for the 135 degree detector offset, the percentages of overlap were under 30%. This pattern was consistent for all time gates (and continuous wave) sensitivity functions considered, and for all cylinder sizes. Figures 3.7 and Figure 3.8 show the percentage agreements for different detector positions for the 2cm and 5mm cylinder sizes, respectively.
Chapter 3. Result

Figure 3.6: the contours of DT, MC-Adj, MC-PT forward model plotted in small size cylinders with different detector placements and time points at TPSF in the same scenario. Red contours are MC-PT; blue contours are normal MC-Adj; cyan contours are isotropic MC-Adj (it is almost the same with normal MC-Adj); black contours are DT. The number in the legend is the area enclosed by contours corresponding to each method.

With respect to early-arriving photons, the DT method agreed better with the MC-Adj method in the large cylinders than in the small cylinders at early time. Example percentage overlaps for 0 degree detector offset for CW, 0 degree detector offset at 10% on the rising edge of the TPSF curve, and 45 degree detector offset at 50% on the rising edge of the TPSF curve are shown in Figure 3.9. Similar results were obtained for the late time sensitivity matrices, but the differences were not as significant as that for early time.
Chapter 3. *Result*

Figure 3.7: Overlap area decrease with the detector moving from 0 degree detector to 135 degree detector in 2cm cylinder for all time-resolved and CW forward models.

Figure 3.8: Overlap area decrease with the detector moving from 0 degree detector to 135 degree detector in 5mm cylinder for forward models at Peak time, 50% falling edge and CW.
3.2.2 Cylinder Results: MC Adjoint vs. the MC Photon Tracking Method

Generally, the MC-Adj method agreed with the MC-PT method better than diffusion theory, especially in large cylinders at late times and for CW cases. However, there are still a few disagreements in some circumstances. For example, in Figure 3.10, the “banana shape” in 3mm cylinder with 135 degree detector placement in CW mode created by MC-Adj and MC-PT are obviously different. The MC-Adj forward model are more like two normally incident pulse lights that intersect in the diffusive medium, whereas MC-PT forward model is smoother in shape from the source to the detector.
Figure 3.10: The figure on the left is created by MC-PT, whereas the figure on the right is created by MC-Adj.

By inspecting Table 3.22 - Table 3.25 for details and quantitative analysis, we can find that the overlaps which are lower than 90% mainly exist at early time in large cylinders (10% rising edge and 50% rising edge row in all the tables below) and small cylinders with large offsets. For the deviations in large cylinders, if we check the contours in previous figures for large cylinder with small angular offset, MC-PT contours are almost enclosed by MC-Adj contours and not as smooth as MC-Adj contours, so either lack of replayed photons or true differences between two methods may cause the low overlap percentages. It remains the same open question as in the slab models. For the small cylinders with large offsets (90 degree detector and 135 degree detector, especially in 135 degree detector case and 3mm cylinder), we believe that normal directions of detectors in MC-Adj cause the differences. From the data in the tables, we can infer that MC-Adj are deviated with MC-PT at early time as well as large angular offsets in small cylinder.

Table 3.22: 2cm Cylinder Overlap (MC-Adj vs MC PT)

<table>
<thead>
<tr>
<th>time</th>
<th>0 degree</th>
<th>45 degree</th>
<th>90 degree</th>
<th>135 degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% rising edge</td>
<td>66.25%</td>
<td>75.81%</td>
<td>69.20%</td>
<td>53.27%</td>
</tr>
<tr>
<td>50% rising edge</td>
<td>85.39%</td>
<td>88.91%</td>
<td>82.13%</td>
<td>64.06%</td>
</tr>
<tr>
<td>Peak</td>
<td>90.03%</td>
<td>92.50%</td>
<td>91.42%</td>
<td>80.95%</td>
</tr>
<tr>
<td>50% falling edge</td>
<td>94.57%</td>
<td>95.48%</td>
<td>96.61%</td>
<td>91.95%</td>
</tr>
<tr>
<td>CW</td>
<td>94.17%</td>
<td>91.56%</td>
<td>88.12%</td>
<td>90.54%</td>
</tr>
</tbody>
</table>
Table 3.23: 1cm Cylinder Overlap (MC-Adj vs MC PT)

<table>
<thead>
<tr>
<th>Time</th>
<th>0 degree</th>
<th>45 degree</th>
<th>90 degree</th>
<th>135 degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% rising edge</td>
<td>78.79%</td>
<td>67.68%</td>
<td>51.58%</td>
<td></td>
</tr>
<tr>
<td>50% rising edge</td>
<td>88.51%</td>
<td>85.17%</td>
<td>78.01%</td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>90.82%</td>
<td>90.30%</td>
<td>89.44%</td>
<td>86.90%</td>
</tr>
<tr>
<td>50% falling edge</td>
<td>94.74%</td>
<td>92.26%</td>
<td>94.00%</td>
<td>90.48%</td>
</tr>
<tr>
<td>CW</td>
<td>92.47%</td>
<td>94.10%</td>
<td>91.51%</td>
<td>80.61%</td>
</tr>
</tbody>
</table>

Table 3.24: 5mm Cylinder Overlap (MC-Adj vs MC PT)

<table>
<thead>
<tr>
<th>Time</th>
<th>0 degree</th>
<th>45 degree</th>
<th>90 degree</th>
<th>135 degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% rising edge</td>
<td>87.50%</td>
<td>82.31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% rising edge</td>
<td>89.87%</td>
<td>85.84%</td>
<td>74.91%</td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>90.93%</td>
<td>87.45%</td>
<td>82.54%</td>
<td>80.54%</td>
</tr>
<tr>
<td>50% falling edge</td>
<td>94.74%</td>
<td>92.26%</td>
<td>94.00%</td>
<td>90.48%</td>
</tr>
<tr>
<td>CW</td>
<td>93.44%</td>
<td>95.98%</td>
<td>90.99%</td>
<td>88.75%</td>
</tr>
</tbody>
</table>

Table 3.25: 3mm Cylinder Overlap (MC-Adj vs MC PT)

<table>
<thead>
<tr>
<th>Time</th>
<th>0 degree</th>
<th>45 degree</th>
<th>90 degree</th>
<th>135</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% rising edge</td>
<td>57.89%</td>
<td>53.51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% rising edge</td>
<td>68.75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td>73.29%</td>
<td>85.14%</td>
<td>75.60%</td>
<td></td>
</tr>
<tr>
<td>50% falling edge</td>
<td>86.96%</td>
<td>85.71%</td>
<td>81.77%</td>
<td></td>
</tr>
<tr>
<td>CW</td>
<td>85.19%</td>
<td>83.43%</td>
<td>75.00%</td>
<td>65.35%</td>
</tr>
</tbody>
</table>

3.3 Irregular Geometry

Similar with the analysis in cylinder models, we first calculated time-resolved and CW forward model for each detector placement, and then plotted contours with the value of the middle point between a source-detector pair for comparison. Figure 3.11 shows the contour results in the irregular geometry.

For comparison between DT and MC-Adj, forward model has more differences in irregular geometry than in large cylinder model, because more boundary conditions need to be considered in photon propagation. Also, it is similar to the result in cylinder model that larger angular offset and early time make more differences.

For comparison between MC-Adj and MC-PT, contours are almost agree with each other. The differences
Figure 3.11: Red line is MC-PT contour. Blue line is MC-Adj contour. Black line is DT contour.
we can see are that MC-Adj curves are smoother than MC-PT curves, especially in the early time (10% rising).

### 3.4 Half and Double Optical Properties in 2cm Slab

With the similar metrics in the 2cm slab with normal optical properties, we compare TPSF, central FWHM and contour area for each set of optical properties. From the Figure 3.12 and Figure 3.13, curves have better agreements in low optical properties slab than in high optical properties slab. Moreover, MC-PT metrics become noisy when the offset is increasing.
Figure 3.12: Results in the 2cm slab model with half optical properties are presented in this figure. Metrics include TPSF, central FWHM and area. The dash lines are value of metrics in CW mode.
Figure 3.13: Results in the 2cm slab model with high optical properties are presented in this figure. Metrics include TPSF, central FWHM and area. The dash lines are value of metrics in CW mode.
Chapter 4

Discussion and Conclusions

4.1 Discussions

In this thesis, we have computed sensitivity functions (also known as “Jacobians”, “weight functions” or “banana functions”) using three different methods: an analytical solution to the diffusion equation (diffusion theory: DT), the Monte Carlo Adjoint (MC-Adj) and the Monte Carlo photon tracking (MC-PT) methods. We computed these for a variety of slab and cylinder models with various thicknesses and detector placements, over a range time points following a short simulated laser pulse. We compared the results according to a number of metrics, including the temporal point spread function (TPSF), contour area, sensitivity function full-width at half maximum (FWHM) in the center of the media, near the sources and near the detectors.

We were particularly interested in the agreement of the resulting calculations for scenarios of ongoing experiments in our lab: namely computation of sensitivity functions at very early time points following a laser pulse [35] [38] [20] and in very small geometries for imaging in mice limbs in DFFC [34]. As described in detail in Chapter 1, MC-PT is believed to be the most physically accurate model, but requires long computation times. MC-Adj is also widely accepted to be an accurate implementation of the RTE and
computes faster than MC-PT (although it is still computationally expensive), but the underlying assumptions may be problematic at early times and small geometries due to the directionality of detectors. DT computes extremely rapidly, but is widely believed to be the least accurate method in the DOT and DFT imaging fields, again particularly at early time points and in small geometries. Therefore, we conducted an in-depth quantitative study in a range of relevant scenarios which, to our knowledge has never been performed previously. However, as we showed, despite the simplifications used in DT (and the additional simplification used here of ignoring boundary conditions), the differences between DT and MC methods for most cases was minimal.

From the results some general patterns of agreement and disagreement were observed.

**Diffusion theory vs. MC-Adj**

1) DT generally agreed well with the two MC methods for large geometry structures and through bulk media, i.e. at the center of the imaging chamber and with respect to the overall contour. In large slabs and large cylinders with detectors placed directly opposite the source, good agreement was observed for both time-resolved and CW forward models between DT and MC methods.

2) As expected at positions very close to sources and detectors (about 10 transport mean free paths) larger disagreement was observed, however, as noted this had a minimal effect on the overall Jacobian contour area due to the relatively small width (FWHM) at these locations.

3) In small slab geometries (less than 5 mm) significant deviations between DT and MC-Adj was observed but only at early time points, i.e. on the rising edge of the TPSF in small slabs.

4) In small cylinder models, less agreement (contour overlap) was observed for larger angle detector placements, presumably due to more significant boundary effects in the photon path from sources to detectors.

5) The degree of agreement (contour overlap) also decreased with decreasing cylinder size.

6) With respect to temporal point spread functions (TPSFs) through slab and cylinder geometries, very good agreement between DT and MC-Adj was also observed.

**MC-Adj vs. the MC-PT**
In general the MC-Adj and MC-PT methods showed excellent agreement due to the overall similarities of the MC method. The methods deviated in only 3 specific conditions:

1) For slab and cylinder geometries at extremely early time points following a laser pulse, this deviated from case to case but in general was at time points earlier than about 10% on the rising edge of the TPSF curve. As we discussed in Chapter 3, the differences are likely primarily due to numerical factors resulting from number of simulated photon packets run. At the early time, MC-PT can only accept hundreds of early photons which may not be enough to create a smooth forward model. In some situations, deviations were observed when MC-PT replayed large numbers of photons, for example in 3mm slab with 3mm offset at 20ps (1841 photons are replayed). In this cases, the discrepancy may be due to the smaller number of photon packets run in MC-Adj simulations. Inspection of the Jacobians (e.g. in Figure 3.3), lends more confidence to the MC-PT result.

2) In small size cylinder geometries (3mm and 5mm cylinders) with large angular source-detector placements, MC-Adj method models photon propagation from two pencil-beam light sources which intersect inside the diffusive medium. The MC-PT method models a more smoothly curved Jacobian which appears more physically accurate. In this case, differences are not likely numerical (because many photons were detected in both cases), and likely realhaha.

3) In terms of the sensitivity function FWHM close to the detector position, this is a result of the finite detector size (\(\frac{1}{10}\) of model size) modeled in the MC-PT method, as opposed to the point source modeled in MC-Adj. While seemingly obvious, this is an effect in real instruments with finite detector sizes and may cause errors in regions close to the surface. For example, our group has noted that time-resolved sensitivity functions in large media is asymmetrical, with higher sensitivity at the side corresponding to the laser source[38]. It should be noted that this could be corrected using the MC-Adj method, for example, by convolving the sensitivity function with a detector, or by launching photons from a distributed source. With respect to our groups ongoing research (i.e. the original goals of this thesis), the following conclusions can be drawn with respect to computing sensitivity functions for each of the three methods we have
studied here.

Time-Resolved DOT and DFT (Early Photon Tomography): Under most practical scenarios for time-resolved small animal fluorescence imaging the use of DT with the assumption of point sources in an infinite media yielded results that were surprisingly in agreement with MC-Adj methods. As such, this is in disagreement with the broadly held view in the time-resolved DOT and DFT fields that MC or higher-order approximations to the RTE are necessary for accurate computation of forward models. Based on our results we conclude that in the case of planar (slab) imaging, DT showed generally good agreements with MC-Adj in large slabs (greater than 1 cm) over all times. As noted above, this was not true very close to sources and detectors, but this had a minimal impact on the Jacobian contour area. However, when imaging with early photons in small size geometries - i.e. on the rising edge of the transmitted TPSF curve in 3mm or 5mm slab - significant disagreement between DT and MC-Adj was observed, (i.e. MC models are preferable).

We further note that our results indicate that under these circumstances and at very early times in larger slab (greater than 1 cm) geometries, MC-PT and MC-Adj also diverge. Review of our data and inspection of the resulting Jacobians imply that MC-PT is more accurate under these circumstances, although we did not explicitly test this under all circumstances. Moreover, for geometries with large source-detector offsets (greater than 45 degree) DT models showed some deviation from MC models but this was minor for slab geometries. In the case of cylindrical geometries, significant deviation between MC and DT was observed for source-detector angles greater than 90 degree. We note that in our latest instrument configuration, angular measurements are made at angles of 90 or smaller, so that again, DT methods are generally appropriate.

Small Geometry DFT (Diffuse Fluorescence Flow Cytometry): Greater deviation was observed for small geometry DFT, and in particular for cylindrical geometries (as opposed to slab geometries). As such, this implies that MC methods should yield more accurate results when performing DFFC imaging[34]. In these specific circumstances review of our data and inspection of the resulting Jacobians imply that MC-PT is
more accurate than MC-Adj. It is also worth re-iterating that our previously published work showed [34] that DT yielded surprisingly accurate results in localizing fluorescently-labeled cells in small geometries. As such, the overall effect of the disagreement between sensitivity functions on the overall reconstructed image quality in DFT or DOT is still an open question and is the subject of ongoing work.

Finally, we note that a major purported advantage of MC versus analytical models of photon propagation (such as DT) is MC’s ability to handle complex geometries with optical heterogeneities, i.e. when multiple organs are in the imaging volume. The effect of heterogeneities was not explicitly considered in this work. However, the “normalized born” field is now broadly employed in DFT imaging, wherein fluorescence data is normalized by the data measured at the excitation wavelength. After this normalization operation, sensitivity functions are computed for homogeneous media using average optical properties. Therefore this advantage in practice is minimal. Moreover, Finite Element solvers allow time-resolved DT to be used in complex mesh geometries with heterogeneities.

4.2 Future Work

In this thesis we compared three methods for modeling photon propagation in slab geometries, cylindrical geometries and in an irregular geometry. However, there are a number of outstanding issues that we did not consider here that could affect the computed forward models by these methods. Therefore, further work will be focused on following issues: First, the performance of the three forward models (especially differences between MC-Adj and MC-PT) should be investigated in more complex or irregular geometries (we only considered one such geometry in this work). Second, the detector size modeled in MC-PT also affects the computed forward model, so the differences between detector sizes are worth further comparison in other geometries. Third, the “isotropic MC-Adj” method mentioned in the Chapter 3 aims at more closely simulating an MC-PT detector where photons can be accepted from many directions (as opposed
to normal to the volume surface). However, in our specific geometries we found that the MC-Adj and Isotropic MC-Adj methods yielded indistinguishable results, which were different than those obtained from MC-Adj. Therefore, we are interested in studying this effect further, i.e. when the two methods may have differences and which is more accurate. Last, most models simulated in this thesis were based on one set optical properties, so comparisons between the three methods in with a wider range of optical properties should also be considered in the future.
Bibliography


