Doctoral Thesis

Modelling light propagation in Tissue

Author[s]:
Böcklin, Christoph

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MODELLING LIGHT PROPAGATION IN TISSUE

A thesis submitted to attain the degree of
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(Dr. sc. ETH Zurich)

presented by
CHRISTOPH BÖCKLIN

Dipl. El.-Ing., ETH Zurich, Switzerland
born on July 16, 1982
citizen of Sins, AG

accepted on the recommendation of
Prof. Dr. C. Hafner, examiner
Dr. J. Fröhlich, co-examiner
Prof. Dr. M. Rudin, co-examiner

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Abstract

Since more than 50 years optical techniques operating in the near-infrared (NIR) wavelength range play an important role in medical applications. The biomedical window between 650 nm to 950 nm, where light absorption by tissue is relatively low, allows light to penetrate a few centimetres into tissue and opens the window for optical diagnosing and treatment applications operating inside tissue. In order to evolve and improve those techniques, it is paramount to understand the mechanisms influencing light propagation in tissue. For this, modelling, simulation and visualisation of these effects are of greatest importance. To date only few techniques exist to simulate light propagation in turbid media. The modelling of light propagation in tissue is a complex interplay between the physical model, an appropriate material characterisation and a method to determine the light propagation in a given material distribution. It is one goal of this thesis to develop a generalised simulation framework in which also most complex structures, such as the human head, can be accurately investigated. Since numerical simulations heavily depend on accurate material parameters, an important part of this work is dedicated to the determination of optical properties and to the development of silicone phantoms whose optical properties can be tailored as desired.

The physical model describing light propagation in turbid media is provided by the radiative transport formalism. Originating in astrophysics, the radiative transport equation (RTE) is capable of tackling the complex structure of tissue by assuming piecewise homogenised materials. The material model employed by the RTE describes the homogenised material with an absorption coefficient $\mu_a$, a scattering coefficient $\mu_s$, a scattering phase-function $p$ (defining the scattering pattern) and a scattering anisotropy $g$. Under certain conditions, these parameters can be related to the commonly used material parameters in electro-magnetics, the permittivity $\varepsilon_r$ and permeability $\mu_r$.

The RTE is a first-order partial differential equation that cannot be solved in a closed form for arbitrary geometries and material distributions. The most general approach to fulfil this task numerically is offered by the Monte-Carlo (MC) algorithm, a randomised statistical sampling technique. A fully three-dimensional general purpose MC simulation framework is developed from scratch in this work. The high computational demand of MC simulations is managed with a parallelised implementation that runs on a cluster infrastructure and enables the simulation of
large anatomical structures. Segmented anatomical images can be imported defining
the spatial material distribution. Refractive index changes between different materi-
als can be appropriately treated due to voxelised computation. A novel and efficient
algorithm is introduced to calculate the three dimensional spatially resolved fluence
rate in arbitrary materials and geometries.

The results from numerical simulations strongly depend on the employed material
parameters. In this work, a procedure is developed which can accurately determine
the optical properties ($\mu_a, \mu_s, g$) as well as the refractive index $n$ of a material. For
this, a double-integrating sphere measurement setup is built and improved with cus-
tom made parts. The careful calibration allows one to determine precise reflectance
and transmittance values for silicone phantom and tissue samples. The reconstruc-
tion of optical parameters from reflectance and transmittance values implies finding
the optimal set of optical parameters that reproduces the measured reflectance and
transmittance values best. A new path is followed by employing a genetic algorithm
to find the optimal solution produced from an MC simulation.

Biomedical applications mostly operate in vivo on animals or directly on humans
where it is often impossible to study the influence of a single parameter on the overall
light propagation. Numerical studies are therefore an indispensable tool to perform
such investigations. A detailed investigation of a multilayered head model will be
performed to obtain answers for certain aspects that are important in near-infrared
spectroscopy (NIRS) measurements. The sensitivity analysis of the absorption coef-
ficients of different layers shows hereby the difficulty for non-invasive NIRS measure-
ments to discover the changes occurring in the brain due to signal contamination in
the superficial layers. A complex head model constructed from magnetic resonance
imaging (MRI) images is introduced. Simulations on this complex model are com-
pared to results from the layered model and show that certain studies have to be
performed on the realistic head model to yield meaningful results.

In vitro measurements are of the same importance as numerical simulations to
characterise and improve optical devices. To date no defined solid reference material
exists that exhibits optical properties similar to those of tissue. A versatile and flex-
ible basis for such phantoms is provided by silicone rubber which can be moulded in
an almost unlimited way to any shape and size of choice. Additionally, the optical
properties can be adjusted by adding scattering and absorption agents to the other-
wise clear silicone. This work will introduce a mixing formula that makes it possible
to manufacture silicone phantoms with defined scattering and absorption properties
by adding defined amounts of the scattering agent TiO$_2$ and the absorption agent
carbon black (CB). Reflectance and transmittance measurements are performed on
multilayered phantom structures. They show excellent agreement to simultaneously
performed MC simulations of the same structures and prove the validity of the mix-
ture formula.
Zusammenfassung


Der Strahlungstransportformalismus wird als physikalisches Modell verwendet, um die Lichtausbreitung in trüben Medien wie Gewebe zu beschreiben. Die Strahlungstransportgleichung (radiative transport equation, RTE) begegnet der komplexen Struktur von Gewebe, indem ein stückweise homogenes Material angenommen wird. Das homogenisierte Material wird vom Materialmodell mit einem Absorptionskoefizienten $\mu_a$, einem Streukoeffizienten $\mu_s$, einer Streu-Phasenfunktion $p$ und der Streu-Anisotropie $g$ beschrieben. Diese Parameter können, unter gewissen Bedingungen, zu den sonst üblichen Materialparametern in der elektromagnetischen Theorie, der Permittivität $\varepsilon_r$ und Permeabilität $\mu_r$, in Beziehung gesetzt werden.

Die RTE ist eine partielle Differenzialgleichung erster Ordnung, die nicht für beliebige Geometrien und Materialverteilungen geschlossen gelöst werden kann. Der allgemeinste Ansatz zur Lösung der RTE wird durch den Monte-Carlo Algorithmus, einer statischtischen Methode basierend auf randomisierten Stichproben, beschrie-

Die Resultate von numerischen Simulationen sind stark von den verwendeten Materialparametern abhängig. In dieser Arbeit wird ein Verfahren beschrieben, welches die genaue Bestimmung der optischen Materialparameter \((\mu_a, \mu_s, g)\) sowie des Brechungsindexes \(n\) erlaubt. Dafür wird ein Messaufbau erstellt, bestehend aus zwei Ulbrichtkugeln, deren Charakteristik mit genau angepassten, selbstgefertigten Teilen verbessert wurde. Die exakte Kalibrierung erlaubt genaue Messungen der Reflexion und Transmission von Silikon-Phantomen und Gewebeproben. Die Rekonstruktion der optischen Parameter aus diesen Reflexions- und Transmissionswerten basiert auf einem inversen Verfahren, das diejenigen Parameter findet, welche die gemessenen Grössen am besten zu reproduzieren vermag. Ein neuer Ansatz dieser Arbeit benutzt dafür einen genetischen Algorithmus um aus Resultaten, die mittels Monte-Carlo Simulationen erstellt wurden, das optimale Parameterset zu finden.


Um optische Geräte charakterisieren und verbessern zu können, sind \textit{in vitro} Messungen ebenso wichtig wie numerische Simulationen. Bis heute sind keine Referenzmaterialien verfügbar, die ähnliche optische Eigenschaften haben wie Gewebe. Eine flexible Grundlage für solche Phantome bietet Silikon, das in praktisch jede Form
beliebiger Grösse gegossen werden kann. Ausserdem können die optischen Eigen-
schaften des klaren Silikon mit entsprechenden Zusätzen verändert werden. In dieser
Arbeit wird eine Mischformel entwickelt, welche die Herstellung von genau definierten
Silikonphantomen erlaubt. Die Absorptions- und Streueigenschaften werden hierbei
mit definierten Mengen von Pigmentruss und Titandioxid verändert. In dieser Weise
wird ein mehrschichtiges Phantom gebaut, an dem Reflexions- und Transmissions-
messungen vorgenommen werden. Die gemessenen Werte werden mit Resultaten von
Monte-Carlo Simulationen der gleichen Struktur verglichen. Die sehr gute Überein-
stimmung der Messwerte mit den Simulationsresultaten bestätigt dabei sowohl die
Richtigkeit der benutzten optischen Parameter und damit der entwickelten Misch-
formel als auch der entwickelten Simulationsumgebung.
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List of Acronyms and Abbreviations

**Numerical Terms**

- 2-D  two dimensional
- 3-D  three dimensional
- AD   Adding-Doubling
- DPF  differential path lengths
- FEM  finite element method
- GA   genetic algorithm
- HG   Henyey-Greenstein
- MC   Monte-Carlo
- MPI  message passing interface
- NA   numerical aperture
- op amp operational amplifier
- RNG  random number generator

**Medical and Physical Terms**

- CB   carbon black
- CSF  cerebro spinal fluid
- CT   computed tomography
- DOT  diffuse optical tomography
- FMT  fluorescence molecular tomography
- Hb   haemoglobin
- HbO$_2$  oxyhaemoglobin
- HHb  deoxyhaemoglobin
- MRI  magnetic resonance imaging
- NICU neuro intensive care unit
- NIR  near-infrared
- NIRS near-infrared spectroscopy
- OCT  optical coherence tomography
RTE  radiative transport equation
SO₂  oxygen saturation
TiO₂  titanium dioxyde
1 Introduction

1.1 History of Biomedical Optics

Optical diagnosis has a long history in medical and biological applications and began with the development of the first light microscopes in the end of the 16th century by dutch glass polishers. For many centuries, the main focus in the development of optical systems was to increase the resolution of optical microscopes, which is ultimately limited by the visible wavelength range at around 200 nm. Yet, the applications have been focused to inspections of the surface of a substance or tissue or the examination of very thin samples of a substance (μm up to mm). Internal anatomical structures and processes were hidden for optical applications due to the high absorption of biological tissue in the visible spectrum. In the beginning of the 20th century, scientists discovered that the absorption properties of blood depend on the oxygen saturation of haemoglobin (Hb) \([2]\). This formed the basis for the development of the pulse-oxymeter, which became an indispensable tool in today’s medical treatments.

The visible red light used in the beginning was replaced by near-infrared (NIR) with invention of infrared filters for photocells during World War II. By using wavelengths in the NIR region it was observed that biological tissue absorbs much less than in the visible light regime. These findings paved the way for today’s applications involving NIR light. Figure 1.1 shows the absorption coefficients \(\mu_a\) for water, oxyhaemoglobin (HbO\(_2\)) and deoxyhaemoglobin (HHb), assuming a water concentration (in tissue) of 72.1%, a total Hb concentration in tissue of 72.5 μmol l\(^{-1}\) and an oxygen saturation (SO\(_2\)) of 70%. It clearly shows the region of relatively low absorption between 650 nm and 950 nm. Therefore this range is often called the biological window \([3]\). In the short wavelength region there is a high absorption from Hb whereas water absorption is predominant above 950 nm. HbO\(_2\) and HHb have distinct absorption spectra due to their structural and molecular differences. The resulting penetration depth (depth at which the incident intensity is reduced to 37% = 1/e \([4]\)) for NIR light in tissue is a few centimetres.

The prospect for new, non-invasive measurement and monitoring techniques exploiting the NIR wavelength region led to a large number of applications in the last decades. The first steps were made by enhancing the idea of the pulse-oxymeter by
Figure 1.1: Absorption spectra of oxygenated blood (HbO$_2$), deoxygenated blood (Hb) and water (H$_2$O). The absorption is comparatively low in the wavelength range from 650 nm to 950 nm, the so called \textit{biological window}.

trying to measure the oxygen saturation directly in the brain [5, 6]. This technique is mostly referred to as near-infrared spectroscopy (NIRS) in literature.

1.2 Applications of Biomedical Optics

Modelling and simulation of light propagation in anatomical structures is important in a number of applications in biomedical optics, hence there is a general interest to understand the mechanisms that influence light propagation. A number of applications that are based on the same principles of biomedical optics are briefly mentioned in the following.

1.2.1 Near Infrared Spectroscopy

Sufficient oxygen supply is of greatest importance for a normal functioning of the brain. Special attention has to be paid to this in neuro intensive care units (NICUs), where brain injuries and bleedings caused by stroke and aneurysms require special measures to dissolve coagulations and hence blood oxygen saturation is often re-
duced. The possibility for a continuous determination and monitoring of the brain oxygenation to guarantee sufficient oxygen supply is therefore paramount.

The first attempt to measure brain oxygenation non-invasively by using NIR light was reported by Jöbsis in 1977 [6]. A large number of people has worked since then on the method that nowadays commonly is referred to as NIRS [7, 8, 9, 10, 11]. NIRS measurements exploit the characteristic and distinct absorption spectra of oxygenated and deoxygenated blood at different wavelengths (see Figure 1.1). Given appropriate reconstruction algorithms, the concentrations of HbO$_2$ and HHb in tissue can be calculated from intensity measurements at different wavelengths. The ultimate goal is to monitor oxygenation of white matter.

In a non-invasive approach [8, 12], laser light in the NIR wavelength range is emitted from a source placed on the scalp. The light is penetrating through skin, skull, cerebro spinal fluid (CSF) layer, meninges and grey matter into white matter and back to the surface where it is detected. Unfortunately, these intermediate tissue layers distort the light signal significantly. Open questions are to what extent the measured reflected light has reached the white matter and hence the clinically relevant region and how to extract brain specific physiological changes from the measured signal. Numerical studies as presented in this work are an essential part in the improvement of the reconstruction algorithms.

Recently, a promising attempt has been made to emit and detect the light directly inside the brain to avoid signal deterioration by the superficial layers [13].

Measurement devices based on NIRS are already used in clinical studies for example in NICUs. A very high specificity and doubtlessness of the employed algorithms and methods is indispensable in such critical usage of a technology. This work will give important answers on certain aspects of NIRS measurements based on numerical studies. The development of defined and reproducible reference materials or phantoms will help to further improve the development and calibration of measurement devices.

### 1.2.2 Diffuse Optical Tomography

The relatively high penetration depth of NIR light compared to visible light allows for trans-illumination of tissue samples with thicknesses up to several centimetres. This is exploited in diffuse optical tomography (DOT) to create tomographic images by means of NIR light.

The basic principles of DOT are very similar to those of X-ray computed tomography (CT), although a completely different wavelength, material model and physical model is employed. The sample to be investigated is illuminated from one side with
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A collimated laser beam and the resulting transmission pattern of the beam is detected at the opposite side of the sample. Illumination and detection equipment are then rotated around the sample (or the sample itself is rotated) until transmission patterns for every angle are assessed. An ideal equipment configuration provides as much circular symmetry as possible.

From the resulting transmission patterns, the spatial distribution of material parameters can be calculated, given appropriate reconstruction algorithms. These algorithms are commonly based on the photon diffusion equation, although improvements have been achieved by directly using the radiative transport equation (RTE) for low-scattering regions [14]. Under optimal conditions, resolutions of 2 mm or even less have been achieved [15]. The resolution achieved by the reconstruction algorithms could be further improved for example by tomographic measurements performed at different wavelengths, a known wavelength-dependence of the optical properties or enhanced numerical models.

One successful application of this technique is used for imaging and diagnosis of the female breasts to detect cancer. Since the employed wavelengths are harmless for the body compared to X-ray, this technique is favourable over CT for frequent examinations.

1.2.3 Optical Coherence Tomography

Optical coherence tomography (OCT) [16] also operates in the NIR wavelength range and attempts to create three dimensional (3-D) high-resolution tomographic images of the first 1-2 mm of the tissue surface [17]. It is based on interference between a reference beam and the reflection from a beam directed on the tissue. The interference intensity contains information on the scattering characteristics of the tissue with a very high depth resolution below 1 μm. Depending on the tissue type, the scattering characteristics will change, hence the amount of backscattered light provides information about the tissue type at a certain position in a certain depth. By scanning the beam over the tissue sample, 3-D tomographic images can be constructed.

The system is limited by the coherence length of the beam in tissue, which is very low since the phase information is lost already after a few scattering events. Nevertheless, it is an established and very useful medical imaging technique since many diseases manifest themselves at the surface of the tissue, such as skin cancer for example. OCT provides a quick and harmless technique to examine the tissue surface.
1.2.4 Fluorescence Molecular Tomography

Fluorescence molecular tomography (FMT) is a novel 3-D optical diagnosing technique based on two dimensional (2-D) fluorescence imaging [18]. A fluorescent agent that selectively binds to a specific molecule or tissue type is excited optically. The emitted light is detected and enables very precise spatial localisation of the corresponding molecule or tissue type. By choosing appropriate fluorescent agents that are excited and emit in the NIR region, the fluorophores can be excited inside tissue of the object in vivo and the emitted light can be detected at the surface of the object. Due to scattering and absorption of both the exciting and emitted light, advanced algorithms are necessary to reconstruct the position of the fluorophore. Hence the better the light propagation inside tissue can be modelled, the more accurate the localisation is. The state-of-the-art reconstruction is based on the approximative diffusion equation [19] which already yields impressive results. More accurate numerical simulations have the potential of supporting and advancing FMT beyond the current state.

1.2.5 Light dosimetry

The ever increasing amount of applications involving light in one or another form also calls for safety assessment and corresponding regulations. Limits for light intensity on the surface of biological objects may not be sufficient to guarantee a certain intensity limit inside tissue. As for electromagnetic radiation in other frequency spectra, dosimetric calculations have to be done for light as well [20, 21]. This work will present a novel method to attain spatially resolved fluence rate maps from Monte-Carlo (MC) simulations. These maps can be used to directly calculate the amount of light in a specific part of tissue if the object is exposed to an external light source.

1.3 Overview over the Thesis

Biomedical applications operating in the NIR wavelength range are based on a complex interplay between the physical model, the material model and algorithms to solve the light propagation in a given setup (see Figure 1.2). The applications usually involve light intensity measurements on the surface of a structure. A backward solution then yields the desired quantities (e.g. Hb concentration or position of a fluorophore) from the measured intensities.

This work is concerned with the physical model and its forward solution since accurate algorithms capable of solving the light propagation in tissue for arbitrary
setups are essential to develop and improve the reconstruction algorithms. Experimental and in vitro measurements along with the development and characterisation of optical phantoms will help to characterise and improve the optical measurement devices.

<table>
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Figure 1.2: Interplay of physical model, material model and forward solution for biomedical applications operating in the NIR wavelength range.

Chapter 2 presents the framework of radiative transport which forms the theoretical foundation to describe light propagation in turbid media. Different analytical and numerical possibilities to solve the RTE are presented. The MC algorithm is the most flexible approach to solve the RTE in any material for arbitrary complex geometries. The important points of the MC algorithm are summarised. For details the reader is referred to literature.

The implementation of the MC algorithm that is developed from scratch in the frame of this thesis is presented in Chapter 3. The novelties such as fully 3-D implementation, parallelisation and the ability to import segmented anatomical images are discussed. A new way to calculate spatially resolved fluence rate maps is introduced. The new algorithm is validated in a setup where the RTE can be solved analytically. It is shown that the new algorithm performs equivalently or even better than the commonly used approach and hence can reduce the computational costs.

A fundamental part of numerical simulations is the employed material model. The determination of the optical properties that characterise tissue and phantom materials is therefore essential. Only a small number of optical properties exists in literature and they show a large variability. Therefore, a measurement setup for optical properties based on integrating spheres is established. Chapter 4 describes
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how the spheres are modified in order to improve the accuracy of the measurements. Since the optical properties cannot be directly calculated from these measurements, an inverse technique has to be applied. The inverse technique comprises a forward solver with an appropriate minimum search algorithm. An analysis of the fitness landscape reveals that multiple isolated minima exist which calls for an evolutionary strategy. A genetic algorithm (GA) is used in combination with a MC model of the true dimensions of the setup. That way, the optical properties of tissue and phantom materials can be reconstructed from reflectance and transmittance measurements with a high accuracy.

Chapter 5 presents a number of numerical examples of the MC code that are relevant in different applications. The analysis and interpretation of optical measurement data in the NIR wavelength region is affected by a large number of uncertainties due to the complexity of the biological structures investigated. By varying certain parameters in numerical simulations, their influence on the total propagation characteristics is investigated. Such variation studies are performed on a layered head model to investigate the influence of a changing absorption coefficient on the total signal. Simulations in complex anatomical structures are performed for a mouse model and for a human head model.

Phantoms mimicking optical characteristics of tissue are an important tool for the development and characterisation of biomedical optic devices. A promising material for such phantoms is silicone. Unfortunately, until now, no specification how to fabricate phantoms with desired characteristics exists. The fabrication and characterisation of solid phantoms based on silicone rubber is introduced in Chapter 6. Scattering and absorption properties of the phantoms can be tailored by adding titanium dioxyde (TiO$_2$) as scattering agent and carbon black (CB) as absorption agent, respectively. A mixture formula is developed that specifies the necessary amounts of TiO$_2$ and CB to obtain the desired optical properties of the phantom. Reflection and transmission measurements are performed on layered phantom structures. These measurements are then compared to results from MC simulations performed on the same structures, with optical properties determined by the mixture formula. Those measurements show that the three components MC simulations, determination of optical parameters, and the manufacturing of phantoms based on the mixture formula produce consistent results.

The thesis is summarised in Chapter 7. Key findings and challenges are pointed out and potential solutions and ideas for future work are given at the end of the chapter.
2 Light Propagation in Biological Tissue

Abstract — The theoretical framework to describe light propagation in turbid media such as tissue is presented in this chapter. The radiative transport equation (RTE) along with the corresponding material model is introduced. The details of light scattering in tissue are discussed and two different approaches to describe the scattering pattern of a particle are mentioned. Possible ways and their limitations to solve the RTE are discussed. An analytical solution for a specific case is introduced and will be used for validation purposes later. Monte-Carlo (MC) is identified as the most versatile general purpose solution algorithm that puts no limitations on either geometry or materials. The most important aspects of the MC algorithm are discussed in the end of the chapter.

2.1 Introduction

The development of reliable optical measurement and diagnosis devices requires a thorough understanding of how light propagates in tissue. The near-infrared (NIR) range allows for penetration depths of a few centimetres, although more exact values have to be calculated for every specific tissue and measurement setup.

The mere structural and chemical complexity of various kinds of tissues prohibit the use of traditional concepts to model electromagnetic phenomena by solving Maxwell’s Equations. In general, tissue exhibits structural features on a wide range of length scales and of arbitrary shape [22] (see Figure 2.1, Molecular Biology of the Cell, 4th Edition). Each of these features may exhibit different permittivities and permeabilities influencing light propagation. Obvious examples are trabecular bone which consists of a sponge-like mesh of bone tissue filled with bone marrow and blood vessels. Even the protein collagen, which acts as structural building block in many different tissue types, may have an influence and cause anisotropic behaviour.

A paradigm shift was introduced in biomedical optics with the radiative transport formalism. The general idea to describe light propagation in terms of photon transport rather than wave propagation was first formulated in the field of astrophysics by Schuster in 1905 [23], where it was used to model light propagation through foggy
atmospheres to explain absorption and emission lines in stellar spectra. A thorough theoretical foundation of radiative transport theory was laid by Chandrasekhar in 1960 [24] and the concept was adopted later on successfully in biomedical optics [25, 26].

Transport theory describes energy transport through a medium containing randomly distributed scattering and absorbing particles, such as tissue, in a heuristic and more phenomenological way than the mathematically rigorous analytical theory of Maxwell. Describing light propagation in terms of photon transport allows for a number of important simplifications to the otherwise very complex system of tissue. Scattering and absorption phenomena are imagined to happen at discrete scattering and absorption sites, with corresponding scattering and absorption cross sections $\sigma_s$ and $\sigma_a$, respectively. It is however very difficult to attribute these scattering sites to specific structures in real tissue. Hence tissue should rather be imagined as a partly homogenised material exhibiting the same effective properties.

In the context of radiative transport, the material (e.g. tissue) is characterised by four parameters, defining its optical properties

- $\mu_a$ absorption coefficient (unit mm$^{-1}$)
- $\mu_s$ scattering coefficient (unit mm$^{-1}$)
- $g$ scattering anisotropy (unit-less, $-1 \leq g \leq 1$)
n refractive index (unit-less, \( n \geq 1 \))

For the sake of completeness, the scattering phase function \( p \), which defines the probability of the scattering angles, should be specified as well. Since mostly the Henyey-Greenstein (HG) phase function is used, which is conveniently parametrised by \( g \), this is often omitted. The optical properties are different for different wavelengths. Hence the choice of a certain set of parameters implicitly defines the wavelength.

The relation of the Radiative Transport formalism to Maxwell’s Equations has been studied by e.g. Ripoll [27] and Fante, where it has been found that the transport formalism is consistent with Maxwell’s Equations if certain conditions are met, e.g. permittivity fluctuations in the medium have to be small compared to unity [28].

### 2.2 Radiative Transport Formalism

#### 2.2.1 Light scattering and absorption by particles

In order to analyse light propagation through a material with randomly distributed particles, scattering of an electromagnetic wave by a single particle is described first. This has been extensively studied by Ishimaru [29], Bohren and Huffman [30] and Mie [31] and is summarised in the following. A summary of the used terms and definitions is given in Appendix A. An electromagnetic plane wave \( \mathbf{E}_i(\mathbf{r}) \) is incident in direction \( \hat{s}' \) on a particle at position \( \mathbf{r} \) (see Figure 2.2). The particle has a generally complex dielectric constant given by

\[
\varepsilon_r(\mathbf{r}) = \frac{\varepsilon(\mathbf{r})}{\varepsilon_0} = \varepsilon'_r(\mathbf{r}) + i\varepsilon''_r(\mathbf{r}).
\] (2.1)
The scattered field in the far-field region \( R > D^2/\lambda \), where \( D \) is a typical dimension of the particle such as its diameter, is given by

\[
E_s(r) = \mathbf{f} (\hat{s}, \hat{s}') \left( \frac{e^{ikR}}{R} \right) \text{ for } R > D^2/\lambda ,
\]

where \( \mathbf{f} (\hat{s}, \hat{s}') \) represents the amplitude and phase of the scattered wave in the far field in direction \( \hat{s} \). The power flux density vectors of the incident and scattered wave are given by

\[
S_I = \frac{1}{2} (\mathbf{E}_I \times \mathbf{H}_I^*) = \left| \mathbf{E}_I \right|^2 / 2Z_0 \hat{s}, \quad S_S = \frac{1}{2} (\mathbf{E}_S \times \mathbf{H}_S^*) = \left| \mathbf{E}_S \right|^2 / 2Z_0 \hat{s},
\]

where \( Z_0 = (\mu_0/\epsilon_0)^{1/2} \) is the characteristic impedance of the medium.

A differential scattering cross section can now be defined as

\[
\sigma_d (\hat{s}, \hat{s}') = \lim_{R \to \infty} \left[ \frac{R^2 S_S}{S_I} \right] = \left| \mathbf{f} (\hat{s}, \hat{s}') \right| = \frac{\sigma_t}{4\pi} p(\hat{s}, \hat{s}') \quad \text{[m}^2/\text{sr]} \]

where \( S_S \) and \( S_I \) are the magnitudes of the power flux vectors in (2.3). The dimensionless quantity \( p(\hat{s}, \hat{s}') \) is called the scattering phase function\(^1\) and will be explained in more detail below. The total observed scattering power at all angles around the particle is called the scattering cross section \( \sigma_s \) and is given by

\[
\sigma_s = \int_{4\pi} \sigma_d d\omega = \frac{\sigma_t}{4\pi} \int_{4\pi} p(\hat{s}, \hat{s}') d\omega
\]

where \( d\omega \) is the differential solid angle.

The total power absorbed by the particle can be expressed in terms of particle cross section \( \sigma_a \). The total cross section \( \sigma_t \) is then given by

\[
\sigma_t = \sigma_s + \sigma_a
\]

and represents the total power loss from the incident wave due to the scattering and absorption of a wave by the particle. The ratio of the scattering cross section \( \sigma_s \) to the total cross section \( \sigma_t \)

\[
W_0 = \frac{\sigma_s}{\sigma_t}
\]

is called the single scattering albedo of the particle.

\(^1\)This has nothing to do with the phase of the field but has its origin in astronomy where it refers to the lunar phases.
The scattering coefficient $\mu_s$ and the absorption coefficient $\mu_a$ are obtained by multiplying the scattering and absorption cross section, respectively, by the density of scatterers or absorbers

$$\mu_s = \rho \cdot \sigma_s$$
$$\mu_a = \rho \cdot \sigma_a$$
$$\mu_t = \mu_a + \mu_s$$ (2.8)

The scattering and absorption cross sections $\sigma_s$ and $\sigma_a$, respectively, are functions of the material properties (e.g. dielectric constant) of the scatterer, the surrounding medium, and the wavelength. It is in general not possible to clearly separate between density and scattering cross section when determining the scattering coefficient in tissue.

### 2.2.2 Radiative Transport Equation

For a given direction defined by a unit vector $\hat{s}$, one can find the average power-flux density of an electromagnetic wave within a unit frequency band centered at frequency $\nu$ within a unit solid angle. This quantity $\hat{I}(r, \hat{s})$ is called the specific intensity [24] (see Figure A.1) and is measured in $W \cdot m^{-2} \cdot sr^{-1} \cdot Hz^{-1}$. It is also called radiance or brightness.

In biomedical optics a laser source with a narrow bandwidth and a detector with a large bandwidth are normally used. Therefore it is more convenient to integrate over the frequency and refer to the following quantity as specific intensity

$$\hat{I}(r, \hat{s}) = \int N(r, \hat{s}) \cdot h \cdot c \cdot d\nu \quad [W \cdot m^{-2} \cdot sr^{-1}]$$ (2.10)

where $h$ is Planck’s constant, $c$ is the speed of light in the medium and $N(r, \hat{s})$ specifies the number of photons per unit volume at position $r$ moving in direction $\hat{s}$. If the specific intensity is the same in all directions at a given point, the radiation field is said to be isotropic.

The radiative transport theory postulates that the energy transported across a surface element $d\sigma$ onto the solid angle $d\Omega$ centred about $s$ is given by [28]

$$d\omega = \hat{I}(r, \hat{s}) (\hat{s} \cdot n) d\Omega d\sigma dt$$ (2.11)

in the time interval $dt$. $\hat{I}(r, \hat{s})$ is the specific intensity of radiation at $r$ in direction $\hat{s}$ that has to solve the radiative transport equation.

Considering the specific intensity $\hat{I}(r, \hat{s})$ being incident upon a cylindrical elementary volume $dV$ with unit cross section $dA$ and length $ds$. The volume $dV = dAds$
contains $\rho dV$ particles where $\rho$ is the number of particles in a unit volume and is called the *number density*. Each particle absorbs the power $\sigma_a \hat{I}$ and scatters the power $\sigma_s \hat{I}$ and, therefore, the decrease of the specific intensity $d\hat{I}(r, \hat{s})$ for the volume $dV$ is expressed as $-\rho dV \sigma_t \hat{I}$.

An increase of the specific intensity $\hat{I}(r, \hat{s})$ is caused by scattering parts of the specific intensity $\hat{I}(r, \hat{s}')$ incident from other directions $\hat{s}'$ into direction $\hat{s}$. (see Figure 2.3).

![Figure 2.3: Scattering from direction $\hat{s}'$ into direction $\hat{s}$](image)

Ultimately, the three-dimensional steady-state radiative transport equation (RTE) is given by [32]

$$
\frac{d\hat{I}(r, \hat{s})}{ds} = -\rho \frac{\sigma_t \hat{I}(r, \hat{s})}{\mu_t} + \rho \frac{\sigma_s}{4\pi} \int_{4\pi} p(\hat{s}, \hat{s}') \hat{I}(r, \hat{s}') d\omega' + S(r, \hat{s})
$$

(2.12)

where the total extinction coefficient is $\mu_t = \mu_a + \mu_s = \rho \cdot \sigma_t$, the scattering coefficient is $\mu_s = \rho \cdot \sigma_s$ and $S(r, \hat{s})$ is a source term at position $r$ in direction $\hat{s}$. The direction in Cartesian coordinates is given by

$$
\hat{s}_x = r \sin \theta \cos \varphi \\
\hat{s}_y = r \sin \theta \sin \varphi \\
\hat{s}_z = r \cos \theta
$$

(2.13) (2.14) (2.15)

and the differential solid angle is given by

$$
d\omega = \frac{r d\theta r \sin \theta d\varphi}{r^2} = \sin \theta d\theta d\varphi
$$

(2.16)
The one-dimensional \((r \rightarrow \tau, \hat{s} \rightarrow \nu)\) and time-independent RTE is given by

\[
\frac{d\hat{I}(\tau, \nu)}{d\tau} = - (\mu_a + \mu_s) \hat{I} + \mu_s \int_{-1}^{1} p(\nu, \nu') \hat{I}(\tau, \nu') d\nu' + \sigma(\tau, \nu).
\] (2.17)

The radiative transport equation is essentially equivalent to Boltzmann’s equation in the kinetic theory of gases.

The RTE is formulated in terms of specific intensity. It does not contain information about polarisation and phase. Therefore all wave phenomena of electromagnetics like coherence and interference are neglected. Although the RTE can be seen as a transport equation for photons, any quantum effects are neglected and they are treated as “intensity pieces”.

### 2.2.3 A note on refractive index

The RTE assumes piecewise homogeneous materials in which the refractive index does not change, or more precisely, where refractive index changes are on such small length scales that they are incorporated into scattering properties. Kumar et al. [33] have derived optical scattering properties directly from refractive index variations of various tissue components. Refractive index changes on the macroscopic level (i.e. between different tissue types) have to be treated separately according to Fresnel’s equations.

### 2.2.4 Scattering phase function

The determination of the exact scattering pattern of an electromagnetic wave incident on an arbitrarily shaped particle is commonly a task for advanced numerical field solvers. Due to the large number of scattering events in tissue and the generally unknown shape and electromagnetic properties of the scatterer, approximations have to be used. In the frame of radiative transport, scattering is separated into a part which determines the probability that a scattering event occurs and a scattering phase function which determines the expected direction of the scattered light.

The scattering profile or scattering phase function

\[
p(\hat{s}, \hat{s}') = p(\nu), \quad \nu = \cos \theta,
\] (2.18)

where \(\theta\) is the angle between \(\hat{s}\) and \(\hat{s}'\), determines the amount of light being scattered at a scattering site \(r\) from direction \(\hat{s}'\) into direction \(\hat{s}\). This scattering angle is a function of several parameters and does not take the field nature of electro-magnetic waves into account. But it gives a probability for the energy to be scattered at a certain angle.
The phase function is treated as a probability distribution and is normalised such that the integral of the phase function over all angles equals unity

$$\int_{4\pi} p(\hat{s}, \hat{s}') \, d\omega = 1$$  \hspace{1cm} (2.19)

where $d\omega$ is a differential solid angle in the $\hat{s}$ direction. This description assumes strictly elastic scattering which means that no energy can be absorbed by the particle. Thus $p(\hat{s}, \hat{s}') \, d\omega$ is the probability that a photon incident from direction $\hat{s}$ will leave in the differential unit of solid angle in the $\hat{s}'$ direction.

The degree of anisotropy of the phase function is described by the expectation value of the scattering angle given by

$$g = \langle \cos \theta \rangle = \langle \nu \rangle = 2\pi \int_{-1}^{1} p(\nu) \nu d\nu = \int_{4\pi} p(\hat{s} \cdot \hat{s}') (\cos \theta) \, d\omega$$ \hspace{1cm} (2.20)

where $g = 0$ denotes isotropic scattering, $g = 1$ solely forward scattering and $g = -1$ solely backscattering media, respectively. A quantity that is often mentioned is the reduced scattering coefficient $\mu'_s$ which describes the amount of isotropic scattering. It is defined as

$$\mu'_s = (1 - g) \cdot \mu_s$$ \hspace{1cm} (2.21)

Certain assumptions have to be made when modelling scattering in tissue. Firstly, only the most dominant effects are considered and an average phase function for a certain kind of tissue is defined. Secondly, scattering events are assumed to be independent of each other such that they can be described with a single scattering phase function, although approximations for multiple scattering in dense media have been derived [34]. The average single scattering phase function is further constrained by assuming that the probability for scattering from one direction $\hat{s}$ into a direction $\hat{s}'$ depends only on the angle $\theta$ between $\hat{s}$ and $\hat{s}'$, thus $p(\hat{s}, \hat{s}') = p(\hat{s} \cdot \hat{s}') = p(\cos(\theta)) = p(\nu)$.

The choice of the phase function has an influence on the propagation characteristics [35]. Hence the question remains, which phase function describes tissue scattering characteristics best. The simplest phase function is the isotropic phase function

$$p(\hat{s}, \hat{s}') = \frac{1}{4\pi},$$ \hspace{1cm} (2.22)

however, it does not model scattering characteristics in tissue in the NIR regime accurately.

Since the size of tissue features is in the same range as the wavelength (650 nm–950 nm), neither the Rayleigh equation nor the ballistic approximation to light scattering are good approximations to be used in radiative transport. Two different
scattering phase functions are used in this work and are explained in the following. An analytical solution to the scattering problem for spherical particles has been derived by Mie [31]. The computation of these solutions require a huge computational effort and are therefore rarely used in tissue optics. A more heuristic description of the scattering profile has been described by Henyey and Greenstein [36], which can be seen as a first order expansion of the Mie solution. This approximation is most often used in calculations of the RTE.

**Mie scattering**

Gustav Mie [31] formulated solutions of Maxwell’s Equations for scattering of a plane electromagnetic wave at an isotropic spherical particle. This solution poses no restrictions on 1) the dielectric properties of the sphere and of the surrounding medium, 2) the wavelength, and 3) the radius of the sphere. If the wavelength is much larger than the sphere radius, the Mie solution approaches the Rayleigh approximation. The opposite case is called the *optical limit* or *ballistic approximation*.

Two parameters are typically used to characterise the system. The size parameter $x$ defines the ratio between the sphere radius $a$ and the wavelength $\lambda = \lambda_0/n_m$ as

$$x = \frac{2\pi an_m}{\lambda_0}, \quad (2.23)$$

and $m$ defines the ratio of the refractive index of the sphere $n_s$ and the surrounding medium $n_m$, respectively

$$m = \frac{n_s}{n_m}. \quad (2.24)$$

Mie found that the amplitude functions of the scattered components of a plane wave at an angle $\theta$ can be written in terms of spherical functions as (following the notation of van de Hulst [37])

$$S_1(\theta) = \sum_{n=1}^{\infty} \frac{2n+1}{n(n+1)} a_n \pi_n(\cos \theta) + b_n \tau_n(\cos \theta))$$

$$S_2(\theta) = \sum_{n=1}^{\infty} \frac{2n+1}{n(n+1)} a_n \tau_n(\cos \theta) + b_n \pi_n(\cos \theta)). \quad (2.25)$$

$\pi_n$ and $\tau_n$ are related to Legendre Polynomials $P_n$ by

$$\pi_n(\cos \theta) = \frac{1}{\sin \theta} P_n(\cos \theta)$$

$$\tau_n(\cos \theta) = \frac{d}{d\theta} P_n(\cos \theta) \quad (2.26)$$
and the Mie coefficients $a_n$ and $b_n$ are given by

$$
\begin{align*}
  a_n &= \frac{\psi'_n(y)\psi_n(x) - m\psi_n(y)\psi'_n(x)}{\psi'_n(y)\xi_n(x) - m\psi_n(y)\xi'_n(x)} \\
  b_n &= \frac{m\psi'_n(y)\psi_n(x) - \psi_n(y)\psi'_n(x)}{m\psi'_n(y)\xi_n(x) - \psi_n(y)\xi'_n(x)}
\end{align*}
$$

(2.27)

where $y = m \cdot x$. $\psi_n(z)$ and $\xi_n(z)$ are related to the spherical Bessel functions $j_n(z)$ and $y_n(z)$ as follows

$$
\begin{align*}
  \psi_n(z) &= zj_n(z) \\
  \xi_n(z) &= z(j_n(z) - iy_n(z)).
\end{align*}
$$

(2.28)

Special attention has to be paid when it comes to the numerical evaluation of $S_1$, $S_2$, $a_n$ and $b_n$ since a numerically stable approximation of the infinite sums has to be found. A successful algorithm is based on the recurrence formulas described by Wang and van de Hulst in [38]. These algorithms have been numerically implemented and will be used later in this work to calculate Mie scattering from TiO$_2$ spheres in silicon.

The scattering amplitude for unpolarised light corresponding to the scattering phase function as defined in (2.18) is given by [30]

$$
p(\cos \theta) = S_{11}(\theta) = \left| S_1(\theta) \right|^2 + \left| S_2(\theta) \right|^2
$$

(2.29)

which corresponds to the scattering phase function value in equation (2.18)

$$
p(\nu) = S_{11}(\nu).
$$

(2.30)

Mie theory allows one to directly calculate the scattering cross section of the sphere, which can then be used to calculate the scattering coefficient in (2.8). From (2.27), the scattering cross section $\sigma_s$ is calculated as follows

$$
\sigma_s = \frac{2\pi a^2}{x^2} \sum_{n=1}^{\infty} (2n+1)(|a_n|^2 + |b_n|^2)
$$

(2.31)

Henyey-Greenstein

Although Mie theory provides a mathematically rigorous derivation of the scattered wave, the most popular choice for a single scattering phase function in tissue is the HG phase function [36], which is given by

$$
p(\cos \theta) = p(\nu) = \frac{1 - g^2}{(1 + g^2 - 2g\nu)^{3/2}}.
$$

(2.32)
It is parametrised with the scattering anisotropy \( g (-1 < g < 1) \), which conveniently is also the expectation value for the scattering angle (see (2.20)). It also fulfils the normalisation requirement defined in (2.19).

Although the HG phase function is the most commonly used one in tissue optics, there might be effects which cannot be completely described by it. Figure 2.4 compares the Mie solution of a TiO\(_2\) particle of variable diameter in a surrounding medium of variable refractive index to the HG phase function with the same expectation value \( g \) for the scattering angle. For some parameter combinations, the HG phase function can sufficiently approximate the Mie solution (Figure 2.4a), whereas for others, the differences are quite large (Figure 2.4b). Nevertheless, the HG phase function serves as a good approximation to the true scattering pattern, since neither the exact shape nor the dielectric properties of the scattering centres in tissue are known. The influence of the phase function on the optical properties of blood have been studied for example by Yaroslavsky [39]. Mourant describes the influence of different scattering phase functions on light transport (comparison between Mie and HG) [35] and even other approximations to the Mie solution have been suggested to be used as phase functions [40].

![Scattering pattern comparison](image-url)
2.3 Solving the Radiative Transport Equation Analytically

Many attempts have been made over the years to solve the RTE in general or to find approximations which are valid when certain assumptions can be made on one or the other parameter of the setup or even on the geometry. But only approximations valid under simplified conditions have been found.

An analytical solution of the RTE for a point source in an infinite homogeneous medium has been derived by Liemert [41] and will be summarised in section 2.3.1.

Analytical approximations for the RTE for the case where the medium is predominantly absorbing or scattering, respectively, have been developed. If absorption prevails, the characteristics of light attenuation are described by the Lambert law [42] who has found the exponential dependence of the intensity on the attenuation coefficient and the thickness. Beer [43] has combined this with varying the concentrations of absorbers. Those findings are commonly referred to as the Beer-Lambert law [44]. If the scattering is much larger than absorption, a photon diffusion equation can be derived from the RTE. Although both approximations have a limited range of validity (see Figure 2.5), they are frequently applied in biomedical optics since they require much less computational effort than other numerical algorithms. A selection of these algorithms is given in Figure 2.10.

In clinical medicine, the integral of the intensity over all directions, called the fluence rate $\phi(\mathbf{r})$ has more practical significance than the specific intensity itself, because an absorbing chromophore at location $\mathbf{r}$ inside the tissue can absorb photons irrespective of their direction of propagation. By definition the fluence rate is given

Figure 2.5: Approximate validity regions of Beer-Lambert and Diffusion approximations.
by

\[ \phi(r) = \int_{4\pi} \hat{I}(r, \hat{s}) d\omega \frac{W}{m^2}. \]  

(2.33)

The following solution algorithms are all formulated in terms of fluence rate \( \phi(r) \).

### 2.3.1 Analytical Solution for a Point Source

For the special case of a point source in an infinite homogeneous medium, Liemert has derived an analytical solution of the RTE [41]. It will be used later to validate the Monte-Carlo (MC) simulation code and is summarised here.

This solution is valid for all combinations of material parameters and is not restricted to a certain range such as the Beer-Lambert law or the diffusion equation. The fluence rate for a point source located in an infinitely extended medium is given by

\[ \phi_0(r) = \sum_{i=1}^{N+1} A_i \exp^{-v_i r} \]  

(2.34)

where \( N \) is the order of the expansion and is set to 19. \( A_i \) is given by

\[ A_i = \frac{1}{b_{N+1}} \frac{P(\lambda_i)}{\prod_{n=1, n \neq i}^{N} (\lambda_i - \lambda_n)} \]  

(2.35)

where the \( \lambda_i \) are the zeros of the polynomial

\[ Q(\lambda) = \sum_{l=0}^{(N+1)/2} b_l \lambda^l = D_{N+1}(\lambda) \]  

(2.36)

recursively defined by

\[ D_{n+1}(\lambda) = (2n + 1)\mu_a D_n(\lambda) + \lambda n^2 D_{n-1}(\lambda) \]  

(2.37)

with \( D_0(\lambda) = 1 \) and \( D_1(\lambda) = \mu_a \). \( \mu_{an} \) is given by \( \mu_{an} = \mu_a + (1 - g^n)\mu_s \) for the case of a HG phase function with anisotropy factor \( g \). The same recursion relation as in (2.37) but with \( D_0(\lambda) = 0 \) and \( D_1(\lambda) = 1 \) leads to

\[ P(\lambda) = \sum_{l=0}^{(N-1)/2} a_l \lambda^l = D_{N+1}(\lambda). \]  

(2.38)
2.3.2 Analytical Approximations

The two most prominent analytical approximations restrict the material to be either mostly absorbing ($\mu_a \gg \mu_s$, absorption limit, tenuous media) or mostly scattering ($\mu_s \gg \mu_a$, diffusion limit, dense media). Even if the properties of tissue are not in one of these ranges, these two approximations find use in many applications.

Beer-Lambert Law

The Beer-Lambert law for a slab is obtained by setting the scattering coefficient to zero in 2.12 and solving for $\hat{I}(\mathbf{r}, \hat{s})$ (or $\hat{I}(d)$ in case of 1-D)

$$\hat{I}(d) = I_0 \exp(-\mu_a \cdot d)$$

(2.39)

where $I_0$ is the initial radiance and $d$ the thickness of the slab (see fig. 2.6). In case

![Figure 2.6: Diminution of the intensity due to absorption as specified by the Beer-Lambert law.](image)

of a single isotropic point source in a homogeneous (infinite) medium and absence of scattering, light propagates only along the direction specified by the source, hence the Beer-Lambert law can be directly written in terms of fluence rate and radius $r$ as

$$\phi_L(r) = P_0 \frac{\exp(-\mu_a \cdot r)}{4\pi r} \quad \text{[W m}^{-2}].$$

(2.40)

If the absorption coefficient $\mu_a$ can be expressed in terms of molar absorption coefficient $\varepsilon$ and concentration $c$ as [43]

$$\mu_a = \ln(10) \cdot \varepsilon \cdot c,$$

(2.41)

the attenuation can be directly expressed in terms of concentration of a substance.
Strictly the Beer-Lambert law is only valid if $\mu_s = 0$. Because of its simplicity, it is, however, frequently used for weakly scattering materials where the absorption coefficient is replaced with the extinction coefficient $\mu_t = \mu_a + \mu_s$.

**Diffusion Equation**

Assuming that $\mu_s \gg \mu_a$, a photon diffusion equation can be derived from the RTE. The complete derivation of the general form of the diffusion equation is given by Ishimaru [29]. The most frequently used case of a point source located at $r$ in an infinitely homogeneous medium is noted here. The diffusion equation in terms of average diffuse intensity $U_d$ is given in this case by

$$\nabla^2 U_d(r) - \kappa_d^2 U_d(r) = -(3/4\pi)\mu_{tr} P_0 \delta(r)$$

where $\kappa_d = \sqrt{3\mu_a\mu_{tr}}$ and the transport scattering coefficient $\mu_{tr} = \mu'_s + \mu_a = \mu_s(1 - g) + \mu_a$. The solution is given by

$$U_d(r) = \frac{\exp(-\kappa_d \cdot r)}{4\pi r} \left[ \frac{3}{4\pi} \mu_{tr} P_0 \right]$$

or in terms of fluence

$$\phi(r) = \frac{P_0}{4\pi D} \exp(-\sqrt{3\mu_a\mu_{tr}} \cdot r)$$

where $\phi(r) = 4\pi \cdot U_d(r)$ and $D = 1/3\mu_{tr}$.

**Diffusion Equation solved with Finite Element Method** In the case of a point source in (infinite) homogeneous medium, the diffusion equation can be solved analytically (see (2.45)). More complicated cases can be solved by using a finite element (FEM) approach [45]. In this work, COMSOL will be used to solve the diffusion equation in an inhomogeneous layered structure (section 5.5.1).

### 2.4 Solving the RTE Numerically

For many biomedical optics applications, approximations with simplified structures and materials are not applicable. The analytical solution and approximations of the RTE are therefore not satisfactory and other solution concepts are required. An
overview over most of the algorithms developed to solve the RTE is given in Figure 2.10. Two methods are particularly suited to calculated light propagation through homogeneous slabs, the Discrete Ordinates method and the Adding-Doubling (AD) method. In this work, the AD method is used to calculate light propagation through slab materials to validate parts of the MC simulation code (section 3.5.1).

The Discrete ordinate method [46] is useful to calculate internal fluence rate. The spatial discretisation consists of a mesh of discrete points \( \{ r_i; i = 1, \ldots, D \} \) and a set of discrete directions \( \{ \hat{s}_j; j = 1, \ldots, M \} \). The integral term of the RTE is transformed into a weighted sum over the directions \( \hat{s} \) with a carefully selected set of quadrature weights \( \{ w_j; j = 1, \ldots, M \} \). The selection of quadrature angles and weights is specially important for strongly anisotropic scattering phase functions. The resulting matrix relation of the quadrature is solved using an iterative scheme. Depending on the material and the number of discretisation angles, unwanted side effects such as spurious rays can occur and are one of the known drawbacks of this method. Other problems concern limitations for highly anisotropic phase functions, which are often encountered in tissue, or numerical difficulties in the quadrature scheme. Some of these limitations have been improved [47] but the method is of limited value as a general purpose solution algorithm.

2.4.1 Adding Doubling

The AD method [48] is advantageous over the Discrete Ordinates method in that it readily provides reflectance and transmittance values for slabs. Requirements are that the geometry consists of homogeneous uniform layers of infinite extent and that the layers are uniformly illuminated. There are no restrictions on the material properties and even layers of different refractive indices can be combined. The AD method assumes knowledge of reflection and transmission for a thin homogeneous layer of the material. Reflectance and transmittance for a layer of twice the thickness of the initial layer is found by summing the contributions from the two individual slabs. As

![Figure 2.7: Nomenclature for the Adding-Doubling method.](image)

in the Discrete Ordinates method, the scattering integral is transformed into a sum
over discrete directions. This allows one to write reflectance and transmittance for a slab of thickness $\tau$ as matrix operators $\mathbf{R}$ and $\mathbf{T}$ and equations for the downward specific intensity $\hat{I}^{1+}$ (see Figure 2.7) as

$$
\hat{I}^{1+} = \mathbf{T}^{01} \hat{I}^{0+} + \mathbf{R}^{10} \hat{I}^{-1}
$$

(2.46)

Although giving straightforward values for reflectance and transmittance of a slab, the method cannot be used for arbitrary three dimensional (3-D) structures. The requirement of uniform illumination can not be met in biomedical applications where a point illumination from a laser or fluorophore is desired.

### 2.5 Monte Carlo

The restrictions of the analytical solution of the RTE and its approximations to solve the RTE in arbitrary materials and complex geometries have been successfully overcome by applying a statistical algorithm to solve the RTE. The MC algorithm [49] is a method to solve a mathematical problem by means of statistical sampling. Wilson has applied this algorithm to the problem of solving the RTE for tissue [4] which was later adapted and extended by e.g. Wang [50], whose MCML code became a standard for 1-D problems.

Statistical sampling in the frame of radiative transport means that the overall light distribution in a medium is determined by calculating the propagation path of a large number of individual photons. However, it is important to note that not an individual photon path has a physical meaning but only a statistically representative ensemble of photon paths. The theory of MC simulations is briefly explained in this section. For more detailed explanation, the reader is referred to literature [4, 50].

#### 2.5.1 Monte-Carlo Algorithm

The most simple algorithm for photon propagation starts with a photon at a specific source position. The photon is propagated in a certain direction (defined by the source) for a fixed step-size, which depends on the material properties of the start position. It is decided upon a drawn random number whether the photon should be scattered or absorbed, depending on the material parameters at the specific position. Yet simple, this approach is very inefficient. Therefore, many attempts have been made to improve this algorithm by different variance reduction techniques [51, 52, 53, 50].

In the photon packet method, a bundle of photons is launched at the same time from the source, i.e. a packet with a certain weight $W_p$. The packet is propagated a variable step-size, depending on the current material parameters. At the new
position, a part of the packet is absorbed, the remaining part is scattered. This procedure is repeated, until the packet weight falls below a certain threshold. To maintain energy conservation, the packet has a certain chance to survive, otherwise it is killed (without the rest weight being absorbed). The effect of this improved

algorithm is illustrated in Figure 2.8. The simulation setup consists of a regular grid with dimensions $50 \times 50 \times 50$ and spacing $0.1 \text{ mm}$ and is filled in one case with a highly scattering and absorbing material with $\mu_a = 1.0 \text{ mm}^{-1}$, $\mu_s = 5.0 \text{ mm}^{-1}$, $g = 0.5$, $n = 1.4$. The material of the second setup has a lower scattering and absorption coefficient $\mu_a = 0.2 \text{ mm}^{-1}$, $\mu_s = 2.0 \text{ mm}^{-1}$, $g = 0.5$, $n = 1.4$. A photon point source is placed at one surface of the cube. The fluence rate is determined on a circular area with radius $1 \text{ mm}$ on the opposite surface. Figure 2.8a shows the relative error for the highly scattering material where a higher packet weight leads to faster convergence (the error measure is described in more detail in section 3.4). Figure 2.8b shows the results for the less scattering and absorbing material where an increase in packet weight has no effect, since the absorption coefficient is much smaller. Only 2-3 interaction events are expected in average over the distance of $5 \text{ mm}$ and the totally absorbed weight is less than the initial packet weight anyway.

2.5.2 Statistical Sampling

In the frame of the RTE, three probability distribution functions, one for the mean free path and two for the scattering angles, are statistically sampled with a particular
sequence of random numbers. For another sequence of random numbers, the results will be slightly different to the first run but comparable within a statistical error. The longer the simulation runs, i.e. the larger the sequence of random numbers considered, the lower this statistical error will be. An acceptable statistical error depends on the problem to be solved. A considerable amount of additional CPU time is needed to reduce this error.

The fast and efficient generation of random numbers is therefore an important part of an MC algorithm. Since series of random numbers are generated by a deterministic algorithm, they are called “pseudo-random numbers”. Hence when it is referred to “random numbers” it is actually meant “pseudo-random numbers”. Requirements for a good random number generator (RNG) are speed of generation, the period before a sequence of numbers is repeated and the correlation of subsequent numbers. The GNU Scientific Library [54] provides a number of implementations of RNGs that will be used in this work.

The algorithms that offer the best quality are those based on the ranlux algorithm. However, in terms of speed they are outperformed by others, for example a Mersenne-Twister based algorithm [55]. These two RNG algorithms are being compared to assess the differences. Both of them are available in the GNU Scientific Library [56] as “mt19937” and “ranlux1”. The relative error is calculated as described in section 3.4 and plotted in Figure 2.9. The relative error for a fixed photon number

![Figure 2.9: Relative error (calculated as described in (3.18)) for two different pseudo-random number generators. The error bars denote the standard deviation of the relative error over all voxels of the grid.](image)

is slightly lower for the ranlux algorithm, however, the Mersenne-Twister based algorithm is almost twice as fast in generating the numbers, which makes the overall performance almost equal for the two algorithms. Because the Mersenne-Twister-
based generator has also a longer period \((2^{19937} \approx 10^{6002})\) it will be used as the RNG for all of the following numerical simulations.

The random numbers \(\xi\) obtained from the RNG are typically uniformly distributed in the interval \([0, 1]\). The sampling of the RTE requires a different distribution, hence these random numbers \(x_i\) have to be expressed by means of samples \(\xi\) drawn from the uniform distribution function. This can be achieved by looking at the cumulative (or integrated) distribution function \(F(x)\) of the desired distribution \(f(x)\)

\[
\xi = F(x) = \int_{0}^{x} f(x)dx,
\]

(2.47)

generating a uniform distribution of random numbers \(y_i\) and then taking the inverse such that

\[
x = F^{-1}(\xi).
\]

(2.48)

In the frame of the RTE it is necessary to sample three different probability distributions. The first one determines the average path a photon is expected to travel before an interaction - absorption or scattering - occurs. The other two concern the photon scattering angle. A summary of the derivation of the sampling of these probability distributions is given in Appendix B.

2.6 Summary

This chapter summarised the theoretical framework that is employed to describe light propagation in tissue. The radiative transport formalism is a phenomenological approach to describe light propagation in complex structures such as tissue. It assumes piecewise homogenised materials that are characterised with an absorption coefficient \(\mu_a\), a scattering coefficient \(\mu_s\), a scattering phase function \(p\), the corresponding scattering anisotropy factor \(g\), and the refractive index \(n\). Refractive index changes between materials have to be treated outside the RTE formalism as will be described in the next chapter. Two different scattering regimes are discussed, the rigorous Mie solution for spherical particles and the commonly used HG phase function.

The analytical solution of the RTE for an isotropic point source in an infinite homogeneous medium is introduced and will be used in the following chapter for validation purposes. The MC algorithm is found to be the most versatile approach to solve the RTE without restrictions on the geometry, the spatial material distribution or the material properties itself. Important aspects of the algorithm were summarised in this chapter. The details of the implementation developed in this thesis are given in the next chapter.
Light Propagation in Tissue

Maxwells Equations

Radiative Transfer Equation (RTE)

Analytical Approximations

General solution attempts

Dense media

Diffusion Approximation

valid if albedo is close to unity, particles mostly scattering rather than absorbing

Tenuous media

Lambert law

valid only for \( \mu_s = 0 \)

Spherical Harmonics Method

\( P_N \)

Expand RTE into series of spherical harmonic functions

Monte-Carlo

Transform RTE into statistical probability density; reproduce statistics by sampling random numbers

Adding-Doubling

Calculate slab reflection and transmission by iterative matrix operations, given reflection and transmission from initial thin slab are known.

Analytical Solution

Solve the RTE analytically for a point source in an infinite, homogeneous medium.

Kubelka-Munk (two-flux)

Two-flux theory assumes isotropic scattering and considers a forward and a backward flux, applicable for 1D problems only.

Four-flux Theory

Extension to two flux theory, introducing two diffuse fluxes in both directions.

Discrete Ordinates \( S_N \)

Scattering integral is approximated by sum over discrete angles, only applicable for certain homogeneous geometries.

Delta-Eddington approach \((g > g_0.7)\)

Phase function split into two terms, a fraction with strongly forward scattering (\( \delta \)-function) and a reduced phase function, applicable to homogeneous slabs only.

Figure 2.10: Concepts to calculate light propagation in tissue
3 Full 3D Simulation of Light Propagation

Abstract — This chapter describes the Monte-Carlo (MC) implementation that was developed from scratch in the frame of this thesis. It is fully three dimensional, parallelised to cope with the high computational demand to get statistically significant results and features the possibility to import segmented anatomical data defining the spatial material distribution. The voxelised computation even allows one to treat refractive index changes between different materials. A novel way to track the fluence rate during the simulation and create spatially resolved fluence rate maps is introduced. It is capable of calculating the fluence rate in any material, even non-absorbing ones. The new algorithm is equally or even more efficient than the traditional way to calculate the fluence rate via absorbed photon power. The voxelised implementation and the new two and three dimensional fluence tracking algorithms are validated with the analytical solution of the radiative transport equation and the Adding-Doubling algorithm in suitable setups.

3.1 Introduction

In this thesis, a three dimensional, fully parallelised Monte-Carlo (MC) simulation framework has been developed to solve the light distribution in large and arbitrarily complex anatomical structures. The requirements to the code were

- three dimensional computation
- parallelised
- ability to import segmented medical data
- treatment of refractive index changes between different tissues within the structure
- efficient spatially resolved fluence rate calculation

Since there were no publicly available codes at the time meeting all requirements (e.g. [50, 57, 58]), it was decided to start a new code from scratch. Some of these requirements have been individually covered in previous work but they are all combined in one implementation for the first time. Missing aspects such as spatially resolved fluence rate maps are added, rendering this MC implementation a powerful
tool to obtain physically meaningful and exact solutions of the radiative transport equation (RTE) in large anatomical structures.

3.2 Implementation

The core of the developed MC code - termed photoncruncher - is a fully object-oriented shared library written in C++. The photoncruncher is a general purpose software not limited to certain application scenarios. While the computationally heavy parts are implemented in the C++ library, the flexibility in using the library is gained from an interface to the python script language. The program flow is defined by python scripts that call corresponding functions of the library.

Figure 3.1 illustrates a typical cycle of a standard MC simulation. The program flow, specially the parts in the dashed square, have to be adapted for the voxelised computation as will be explained in the following.

3.2.1 Parallelisation

One major burden of MC simulations are the generally high computational costs since achieving small statistical errors requires a huge amount of simulated events. In the context of the RTE, this amount additionally depends on simulation parameters like the size of the computational domain and the optical parameters of the tissues. Improvements in speed can be achieved on the algorithmic side with the “photon packet” technique [50] and on the software side by carefully profiling the code to identify computationally expensive parts that need to be optimised [59].

Yet, in order to be able to simulate large volumes like the human head it is inevitable to parallelise the code to achieve reasonable simulation times. Recent implementations make use of graphics card processors (GPU) which provide large numbers of parallel threads [60, 58, 61]. In the framework presented here, a message passing interface (MPI) [62] parallelisation scheme has been implemented. With MPI, processes can be spread over different machines in a cluster and adaptations to the code are not necessary for different cluster environments. MC algorithms are very appreciative for parallelisation, since they consist of a series of independent processes which do not depend on results from previous calculations.

Each of the parallel processes of the simulator has its own random number generator (RNG) engine seeded with the individual MPI process number. For the current maximal number of parallel processes, 256, this approach is reasonable since no correlation or re-usage of the random number sequence can be observed when analysing the progression of the statistical error (see Figure 3.2).
Figure 3.1: Program flow of photoncruncher for the photon packet method. The part in the dashed square is adapted in the stepping algorithm and explained below.

The parallelised code speeds up virtually linearly with the number of processes (cores) available. Still, it has to be taken care, that the partial results from the different processes are correctly reduced and saved for post-processing. After every doubling of the photon number, the master process collects the partial results from
FULL 3D SIMULATION OF LIGHT PROPAGATION

Figure 3.2: Convergence error for a sample setup run on 1 core and run on 128 cores. The error evolution is the same for both simulations, hence there is no correlation between the RNGs seeded with the process number.

Figure 3.3: Relative intensity and relative error shown for the same simulation setup, run on different number of cores for a fixed photon number of $6.71 \times 10^9$. The results show that the same relative intensity is obtained irrespective of the number of processes. The relative error is in the same range for all simulations.

3.2.2 Simulation Time

Giving an estimation for the total runtime of a simulation is not that simple since it depends on the material parameters, the required statistical error limit, the initial
photon packet weight and the geometrical configuration. Figure 3.4a shows the

(a) Simulation time for a fixed number of photon packets and different material parameters

(b) Simulation time needed to achieve a certain minimal statistical error.

Figure 3.4: Comparison of the required simulation time for a fixed photon packet number (left) and for a fixed minimal statistical error (right).

simulation time (logarithmic scale) required to simulate a fixed number of photon packets in a given sample setup. As expected, the time increases for increasing scattering or absorption coefficients. However, if both scattering and absorption coefficients are high at the same time, the simulation time decreases again, since the photon packets are very quickly absorbed. A better time estimation is obtained by looking at the minimal statistical error that should be achieved at a certain position. This value is shown in Figure 3.4b for different the material parameters combinations. The required time is now very much increased if both the absorption and the scattering coefficients are high.

3.2.3 Input Geometry and Material Distribution

The input geometry is essentially the spatial information of the material distribution in the MC computational domain. It is defined on a regular grid, since the main field of application is to simulate light propagation in structures reconstructed from MRI/CT data, which inherently contain grid-based information. A regular grid is also favourable in terms of computation speed. Nevertheless, arbitrary geometries and material distributions can be defined in such a structured computational domain.

Although the basic MC algorithm does not inherently rely on a structured grid, the voxelised implementation requires a grid structure which defines the extent, the grid
spacing, and the origin of the computational domain. Material information can be defined as per voxel. The photoncruncher can import geometries that are stored in \textit{vtk} files. This offers a straightforward way to import segmented magnetic resonance imaging (MRI) images, e.g. to simulate realistic head structures.

\subsection*{3.2.4 Boundary Conditions}

Up to now there exist two different boundary treatments. Since a boundary mimicking an infinite extent of the material is not (yet) available, a completely absorbing boundary is implicitly assumed at the end of the computational domain since every photon packet leaving the domain is killed. Hence the computational domain has to be chosen large enough such that boundary effects are negligible.

A completely reflecting boundary can be achieved by defining a thin material layer with a refractive index $> 100$, which is internally treated as completely reflecting boundary.

\subsection*{3.2.5 Sources}

The photoncruncher features three types of sources for light intensity generation. Since the RTE is formulated in terms of specific intensity, the sources generate incoherent light without information about phase or polarisation.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{source_types.png}
\caption{The three different source types available in photoncruncher: a) isotropic point source, b) point source, c) beam source with Gaussian beam profile.}
\end{figure}

\begin{description}
\item[Isotropic Point Source] The most basic source type is an isotropic point source. It launches photon packets in random directions over $4\pi$ solid angle.
\item[Point Source] The photon point source launches photon packets in a specific direction from a point in space. If a numerical aperture (NA) is specified, the
\end{description}

\footnote{\url{www.vtk.org}}
photons are launched in a certain range of solid angle, given by the numerical aperture as

$$\alpha = \arcsin \left( \frac{\text{NA}}{n} \right).$$ (3.1)

where $n$ is the refractive index of the surrounding medium of the source.

**Gaussian Beam Source** A more realistic source type is provided by the Gaussian beam source. Photon packets are launched over a certain area mimicking a Gaussian Beam at the source. The further propagation is determined by the RTE and not by Gaussian beam optics. The position of the launched photons is determined by the uncorrelated bivariate normal distribution

$$f(x, y) = \frac{1}{2\pi\sigma_x\sigma_y} \exp \left( -\frac{1}{2} \left[ \frac{(x - \mu_x)^2}{\sigma_x^2} + \frac{(y - \mu_y)^2}{\sigma_y^2} \right] \right)$$ (3.2)

where $\mu_x = \mu_y = 0$ with respect to the origin of the source and $\sigma_x = \sigma_y = r = w_0$ corresponds to the radius or the beam waist of the beam.

The wavelength of the light emitted by the source is implicitly defined by the choice of material parameters since they are wavelength dependent. Hence all material parameters have to be chosen for a specific wavelength. The determination of optical parameters for different wavelengths and their dependence on the wavelength are described in the next chapter.

### 3.3 Fluence Tracking

The fluence rate, as any other quantity of an MC simulation, is derived from the ensemble of simulated photon paths. Due to the vast amount of data it is not an option to store all the photon paths for post-processing, hence the desired quantities of a simulation have to be tracked during the simulation run.

#### 3.3.1 Voxelised computation

In order to be able to obtain spatially resolved values for absorption and fluence, the algorithm described in section 2.5.1 has to be adapted. For the novel spatially resolved fluence rate calculation described in section 3.3.3 it is necessary to know the partial path lengths the photon packet travels in every voxel. Instead of the free space photon packet method, a voxelised computation has to be used. Furthermore, to be able to treat refractive index changes between different materials appropriately, photon packets have to be propagated voxel by voxel.
Figure 3.6: The two different algorithms, the traditional free space photon packet method and the voxelised stepping algorithm

The voxel size is defined by the input material grid defining the geometrical structure, which also defines the dimensions of the analysis grid. Similar to the free space method, a variable stepsize is calculated based on a random number and the material properties at the start position. The photon packet is then propagated to the voxel boundary and this path length is registered in the analysis grid. The photon packet is subsequently propagated from voxel boundary to voxel boundary. If the material changes from one voxel to the next, the stepsize is rescaled according to the new material properties. The voxel stepping is performed until the total stepsize has been propagated. The photon packet is then partly absorbed and scattered and the procedure is repeated with a new stepsize (see Figure 3.6). Figure 3.7 illustrates the adapted program flow for the voxelised computation.

**Treatment of refractive index changes**

As described in section 2.2.3, refractive index changes between different materials at voxel boundaries have to be treated separately. They are treated as specified by Fresnel’s equations, where the reflection coefficients for s- and p-polarised light are given by

\[
R_s = \frac{n_A \cdot v_i - n_T \cdot \sqrt{1 - \left(\frac{n_A}{n_T} \sin^{-1}(v_i))\right)^2}}{n_A \cdot v_i + n_T \cdot \sqrt{1 - \left(\frac{n_A}{n_T} \sin^{-1}(v_i))\right)^2}}
\]

(3.3)
Figure 3.7: The voxelised algorithm contains an inner loop, where the total step size $\Delta s$ is incrementally reduced by stepping from voxel boundary to voxel boundary.

$$R_p = \left[ \frac{n_A \sqrt{1 - \left( \frac{n_A}{n_T} \sin(\cos^{-1}(v_i)) \right)^2 - n_T \cdot v_i}}{n_A \sqrt{1 - \left( \frac{n_A}{n_T} \sin(\cos^{-1}(v_i)) \right)^2 + n_T \cdot v_i}} \right]$$ (3.4)
and for unpolarised light

\[ R = \frac{R_s + R_p}{2} \quad (3.5) \]

where \( u_i = \cos(\theta_1) \).

In a pre-processing step, the material grid is analysed and changes of the refractive index in neighbouring voxels are identified and marked by setting the bit corresponding to the face to 1. Such, it can be quickly checked during the simulation if a refractive index change occurs at a certain face of the voxel. If a photon packet is about to cross a voxel face with a refractive index change during the simulation, a random number is drawn. If it is smaller than \( R \), the photon is reflected, otherwise it is transmitted.

In case of reflection, the new direction is calculated based on the assumption that the reflection is specular as (see Figure 3.8)

\[ I_r = I + 2 \times (N \cdot I) \times N \quad (3.6) \]

In case of transmission, the new direction is given by

\[ I_t = \left( \frac{n_1}{n_2} \right) I + \left( \frac{n_1}{n_2} \cos \theta_1 - \cos \theta_2 \right) N \quad (3.7) \]

where

\[ \cos \theta_1 = \frac{N \cdot I}{|N||I|} \quad (3.8) \]

and

\[ \cos \theta_2 = \sqrt{1 - \left( \frac{n_1}{n_2} \right)^2 (1 - (\cos \theta_1)^2)}. \quad (3.9) \]
Different Spacing in different directions

In structures derived from MRI images, the grid spacing is often not isotropic. Therefore it must be possible to set different spacings for x, y, and z directions, respectively. This can potentially introduce errors in the implementation and hence the isotropy of the source and the algorithm in a not equispaced grid is verified. For this, a simulation of a square block with edge length of 1 cm, dimensions of $10 \times 20 \times 10$ and spacing of 1.0, 0.5, 1.0 (see Figure 3.9a) is performed. The dimension and spacing is different in y-direction (but the total extent is the same in every direction). Rectangular detectors with dimensions of $2 \times 1 = 2 \text{mm}^2$ are placed on each face of the block. An isotropic point source is placed in the centre of the block. Figure 3.9b shows that the relative intensity converges to the same value for all six detectors after a certain photon number as expected, despite of the different spacing in y direction.

3.3.2 2D Fluence Rate

The two dimensional (2-D) fluence rate is calculated with respect to a specific area. In the most general form it is an infinite detector plane, counting the weights of all the photon packets crossing the plane in the correct direction. The fluence rate is
formally defined by

\[
\phi = \frac{N}{A}
\]  

(3.10)

where \(N\) is the number of photons incident on an area \(A\). In the frame of the MC code this means that the fluence in the specific area is obtained by summing the weights \(w_i\) of all photon packets crossing the area

\[
\phi = \frac{\sum w_i}{(N \cdot W) \cdot dA} \left[ \frac{W}{m^2} \right].
\]  

(3.11)

where \(N\) is the number of launched photon packets and \(W\) is the initial weight of a photon packet. The shape of the detector plane can be more specific, such as circular or rectangular (see Figure 3.10), corresponding the numerical implementation of real photo-detector shapes.

The detectors can be configured such that they selectively detect photons which have passed a certain position or material in the geometry. This is useful to analyse the influence of a specific region on the total fluence rate and will be used in section 5.5.2 to calculate the ratio of the signal that has penetrated to a certain depth to the total detected signal.

After every step of a photon packet it has to be checked whether it crossed a detector plane or not. A computationally efficient way to achieve this is offered by using Plücker coordinates which are especially suited to solve the line–plane intersection problem. They are frequently used in computer graphics and have been successfully applied also in other Monte Carlo codes [63, 64].

Figure 3.10: Different detector types in photoncruncher: a) (infinite) detector plane, b) rectangular detector and c) circular detector.
The results of the detectors can be saved at the end of a simulation run or after every doubling of the photon number. This enables the possibility to analyse the evolution of the statistical error as described in section 3.4.

### 3.3.3 3D Fluence rate

It is often desired to obtain a spatially resolved fluence distribution from MC simulations. Light dosimetry for example requires the fluence rate to be calculated in the whole geometry to obtain information about light intensity at a particular point within the tissue. A spatially resolved fluence distribution is also helpful to gain general insights on the role and importance of certain structures or materials on the total light propagation (e.g. light piping an aqueous layers).

Commonly [57, 64], the fluence $\phi$ is derived from the spatially resolved number of absorbed photon packets

$$\phi = \frac{P_A}{\mu_a}.$$  \hspace{1cm} (3.12)

Consider the thought experiment of an evacuated box with totally reflecting boundaries (perfect white walls): If a single photon packet is launched in the center of the box, it should bounce around in the box forever and the fluence rate should eventually become uniform in the whole box. Although the approach in (3.12) is straightforward, it is unpractical for materials with a low or zero absorption coefficient such as cerebro spinal fluid (CSF) and would fail in the situation described above. Hence another way to determine the fluence rate is needed. A novel way to calculate the fluence rate directly from photon packet trajectories is developed in this thesis and is explained in the following.

The fluence rate can also be calculated from the sum of the path lengths $dl_i$ in the volume $dV$ [65]

$$\phi = \frac{\sum dl_i}{dV}.$$  \hspace{1cm} (3.13)

This means that the fluence in a voxel is obtained by summing over all partial photon packet paths that fall within that voxel

$$\phi = \frac{\sum dl_i \cdot w_i}{dV \cdot (N \cdot W)} \left[ \frac{W}{m^2} \right].$$  \hspace{1cm} (3.14)

where $dV$ is the volume of the voxel, $w_i$ is the current weight of the photon packet $i$, $N$ is the total number of simulated photon packets and $W$ is the initial weight of a photon packet [66].
The step size $\Delta s$ for a photon packet is calculated based on the material properties at the start point. In order to obtain the partial path length $d_l$ of the photon packet within the voxel, it has to be propagated from one voxel boundary to the next one, decreasing the original step size by the path length $d_l$ within the voxel $\Delta s' = \Delta s - d_l$. By propagation from voxel boundary to voxel boundary, it is also possible to treat refractive index changes at the voxel boundaries as described in section 3.3.1. A further improvement of the code and speed-up of the simulation could potentially be achieved by drawing a new random number and generating a new step size thereof at a voxel boundary instead of decreasing the original step size.

The path length $d_l$ of the photon packet with power $dP = \frac{d\omega}{4\pi dV}$ within the voxel is summed up, according to (3.14). Figure 3.11 illustrates three exemplary photon trajectories within a voxel.

![Example photon trajectories](image)

Figure 3.11: Exemplary photon trajectories within a voxel: a) In the absence of a scattering or absorption event, the fluence of the voxel is increased by $d_l dP$. b) If scattering and/or absorption occurs in the voxel the fluence of the voxel is increased by $d_l dP_1 + d_l dP_2$, c) In the situation where the photon is reflected at a voxel boundary with refractive index changes and a scattering and absorption event, the fluence of the voxel is increased by $\frac{(d_l + d_l) dP_1 + d_l dP_2}{dV}$.

If a photon is crossing a voxel without interaction, the fluence of the voxel is increased by

$$\frac{d_l dP}{dV}$$

(3.15)

(see Figure 3.11a). If the photon is scattered within the voxel (and has a part of its weight absorbed at the same time), the fluence is increased by

$$\frac{d_l dP_1 + d_l dP_2}{dV},$$

(3.16)

where $P_2 \leq P_1$, depending on the absorption coefficient (see Figure 3.11b).
If the photon encounters a refractive index change at a voxel boundary (see Figure 3.11c) and is reflected and subsequently scattered and partly absorbed, the fluence is increased by

\[
\frac{(dl_1 + dl_2) dP_1 + dl_3 dP_3}{dV}.
\]

(3.17)

This results in a spatially resolved three-dimensional fluence rate distribution in the whole computational domain. The algorithm allows for photon packet propagation and efficient fluence rate calculation even in weakly or non-absorbing media, despite of the infinite step size $\Delta s$ which is caused by absorption and scattering coefficients equal to zero. Source and detectors can therefore be placed outside of solid objects in the computational domain, which is often the case when comparing simulations to measurements, where photo-detectors are placed mostly outside the object or tissue.

For time-resolved simulations, the algorithm would have to be adapted to attribute different segments of a photon packet trajectory not only to a certain voxel but also to a certain time range.

3.4 Statistical convergence

The photoncruncher saves intermediate simulation results after every doubling of the number of simulated photon packets. The total photon weight $W_{N+1}$ of a detector or in a voxel at step $N + 1$ can then be compared to the value $W_N$ with half the photon packet number. Since the number of photons has been doubled, the detected value should also be doubled. The relative statistical error can thus be calculated by

\[
\varepsilon_s = \left| \frac{W_{N+1}}{W_N} - \rho \right| \rho
\]

(3.18)

where $\rho = \frac{P_{N+1}}{P_N}$ is the ratio of the exact number of simulated photons at step $N + 1$ and $N$, respectively (depending on the number of parallel processes, this might not exactly be 2).

Figure 3.12 shows the convergence of the statistical error for a sample setup run on 128 cores along with a fitting of the data. A halving of the statistical error roughly requires an increase of the number of simulated photon packets by a factor of 8. These numbers are estimations for this specific setup and have to be analysed for each setup anew.
Figure 3.12: Statistical convergence of a sample simulation run on 128 cores.

### 3.5 Validation

Validation of the newly introduced aspects of the MC algorithm is performed with two different setups. The first setup is used to validate the treatment of refractive index changes in the geometry and the 2-D fluence tracking with detector planes. It consists of a slab material with two detector planes. Reflection and transmission of slab material including refractive index changes can be calculated for example with the Adding-Doubling (AD) algorithm, hence reflection and transmission from the MC simulation are compared to results obtained from the AD algorithm for the same structure.

The second setup is used to validate the three dimensional (3-D) fluence tracking algorithm. It consists of a point source in a block of homogeneous material. The fluence rate in such a setup can be calculated with the analytical solution of the RTE (see section 2.3.1). The analytical solution assumes an infinite medium, hence the computational domain has to be large enough such that boundary effects can be neglected.

The validation cannot be performed for all possible materials or combinations of optical parameters. A number of materials covering the range of optical properties found in tissue have been evaluated. The results are comparable and results for one representative material have been selected for both setups and is shown in the following.
3.5.1 Validation with Adding-Doubling

The correct treatment of refractive index changes in the voxelised computation of the MC algorithm is validated by comparing reflectance and transmittance values from a thin slab in air to results from AD, which itself is able to reproduce values from analytical calculations by van de Hulst [67]. Figure 3.13 shows the setup for the validation. A slab material with refractive index higher than 1 is placed in air. A point source located in air illuminates the slab with a collimated beam. Due to the voxelised computation, the refractive index change is detected and appropriately treated. The reflectance $R_{\text{mc}}$ and transmittance $T_{\text{mc}}$ obtained from the MC simulation are the ratio between the detected weights $w_R$ and $w_T$ compared to the total weight launched from the source $W_{\text{tot}}$

$$R = \frac{w_R}{W_{\text{tot}}} \quad (3.19)$$
$$T = \frac{w_T}{W_{\text{tot}}} \quad (3.20)$$

The relative error between the MC simulation $R_{\text{mc}}$, $T_{\text{mc}}$ and the results from AD $R_{\text{ad}}$, $T_{\text{ad}}$ are calculated as follows

$$\varepsilon_R = \frac{|R_{\text{ad}} - R_{\text{mc}}|}{R_{\text{mc}}} \quad (3.21)$$
$$\varepsilon_T = \frac{|T_{\text{ad}} - T_{\text{mc}}|}{T_{\text{mc}}} \quad (3.22)$$

The results from one simulation with material properties of $\mu_a = 0.1 \text{ mm}^{-1}$, $\mu_s = 5.0 \text{ mm}^{-1}$, $g = 0.5$, $n = 1.4$ are plotted in Figure 3.14. The reflectance and the
3.5.2 Validation with Analytical Solution

An MC simulation of a cubical computational domain with side length $A = 50 \text{mm}$ and filled with a homogeneous material is performed. The optical properties of the material are $\mu_a = 0.05 \text{mm}^{-1}$, $\mu_s = 2.0 \text{mm}^{-1}$, $g = 0.0$. An isotropic point source is located in the centre. The fluence is tracked in a regular grid as described above. The values obtained in the voxels on the diagonal of the block (see Figure 3.15b) are compared to the values from the analytical solution of the RTE described in section 2.3.1 evaluated at the centre of the voxels. The outermost voxels are ignored due to different boundary treatment of the MC code compared to the analytical solution. The analytical solution assumes an infinite geometry whereas the computational domain of the MC solver has to be truncated at some point, mimicking an absorbing boundary. The analysis grid has the resolution $D = 50$ and the spacing $\Delta a = A/D = 1 \text{mm}$.

Figure 3.16a shows the absolute fluence rate on the diagonal of the block in Figure 3.15b, once calculated with the analytical solution of the RTE at the centre of the
Figure 3.15: Computational domain employed for comparison of MC simulations with analytical approximations. a) An isotropic point source is located in the centre of the domain. b) Voxels where the average intensity computed with the analytical approximations are compared to the MC simulation results.

(a) The absolute fluence rate on the diagonal of the block in figure 3.15b, calculated with the analytical solution of the RTE at the center of the voxel and with the MC fluence tracking algorithm.

(b) The relative error between MC results and the analytical solution.

Figure 3.16: Absolute fluence rate (left) and relative error (right) of the fluence tracking algorithm compared to the analytical solution.
can reproduce the analytical solution very good with an error of less than 3% (except for the voxels very close to the source).

3.6 Performance

The performance of the new algorithm is analysed by comparing the simulation results of both fluence and absorption tracking algorithms (as described in (3.12)) in the same setup as in 3.5.2 to the analytical solution (section 2.3.1) and calculating the mean relative error after every doubling of the number of simulated photon packets. The mean relative error over all voxels on the diagonal (fig. 3.15) is calculated by

$$E_r = \frac{\sum_i |\phi_{MC}^i - \phi_A^i|}{\phi_A^i N_i},$$

where $\phi_A^i$ is the value from the analytical solution of the RTE evaluated at the centre of voxel $i$, $\phi_{MC}^i$ is the value from the MC simulation and $N_i$ is the number of voxels considered.

The simulation was run on a cluster with 128 cores. Figure 3.17 shows the convergence of the mean relative error $E_r$ averaged over the voxels $i$ on the diagonal for a grid spacing of 0.2mm compared to the total simulation time. The new algorithm and absorption tracking perform alike for a low photon number (i.e. short simulation time), but as the relative error decreases, the new algorithm performs better.

Figure 3.17: The relative error between the simulation and the analytical solution averaged over the voxels on the diagonal for a grid spacing of 0.2mm and a material with $\mu_a = 0.05 \text{ mm}^{-1}$, $\mu_s = 2.0 \text{ mm}^{-1}$, $g = 0.0$. 
If the ratio between the mean interaction length $1/\mu_t$ and the grid spacing is further increased (i.e. longer interaction length and smaller grid spacing), the new algorithm converges faster than absorption tracking. Figure 3.18 shows the convergence of the mean relative error of the voxels on the diagonal for a grid spacing of 0.2 mm and a material with $\mu_a = 0.1 \text{ mm}^{-1}$, $\mu_s = 1.0 \text{ mm}^{-1}$, $g = 0.0$. The new algorithm (brown squares) converges faster to the analytical solution than absorption tracking.

In case of absorption tracking, the probability of a fluence increase (absorption and scattering event) from a photon packet traversing a voxel depends on $\mu_t = \mu_a + \mu_s$ and the voxel size. The smaller the voxel size compared to the mean interaction length $1/\mu_t$, the lower the probability for a scattering and absorption event and hence the lower the probability that the photon packet contributes to a fluence increase. In case of the new fluence tracking, a photon packet traversing a voxel always contributes to a fluence increase, regardless of whether a scattering and absorption event occurs in the specific voxel.

Albeit the slightly increased computational demand of the new fluence tracking algorithm compared to absorption tracking, it converges faster for materials where the mean interaction length $1/\mu_t$ is larger than about $2 - 3$ times the grid spacing. A grid with a spacing smaller than the mean interaction length can be desirable to increase the resolution. It can even be necessary for complex geometries if one or several materials have interaction lengths much larger than the voxel size and the
interaction lengths of the other materials (an example hereof is the CSF layer in the head for which the interaction length is much larger than the grid resolution determined by the MRI image).

3.7 Summary

The implementation details of the photoncruncher are covered in this chapter. Figure 3.19 demonstrates a sample simulation performed with the photoncruncher. The computational domain contains two blocks of scattering material surrounded by air. An observer rectangle is placed between the source and the scattering blocks. The spatially resolved 3D fluence (colored) is shown along with a few photon packet sample paths from the point source.

Figure 3.19: Sample MC simulation setup with point source with a numerical aperture of 0.5. The computational domain contains two blocks of scattering material surrounded by air. An observer rectangle is placed between the source and the scattering blocks. The spatially resolved 3D fluence (colored) is shown along with a few photon packet sample paths from the point source.

The parallelised implementation of the photoncruncher allows one to compute the light distribution in large volumes on cluster infrastructures with several hundred cores. The fluence rate can be tracked on two dimensional planes, rectangles and circles. Spatially resolved three dimensional fluence rate maps as visualised in the above figure can be created. The novel algorithm enables the efficient calculation of accurate fluence rate values also in weakly and non-absorbing materials. The
validation of the implementation and the new algorithm shows a good agreement between the analytical solution and the three dimensional fluence tracking. Similar validation results are obtained for the two dimensional fluence rate and treatment of refractive index changes, which are validated with results from the Adding-Doubling algorithm.
4 Determining Optical Properties

Abstract — This chapter explains the necessary steps to determine optical properties of tissue and phantom materials employing double integrating sphere measurements. The ready-made spheres are improved with custom parts to improve the sensitivity and are carefully calibrated with reflection and transmission standards, respectively. A new procedure is introduced for the parameter reconstruction. Unique solutions from the reconstruction algorithm are obtained by measuring the same sample at different thicknesses. An accurate Monte-Carlo model that is able to account for the light losses between the sample and the sphere is constructed to calculate reflectance and transmittance of a given set of parameters, including the refractive index. A genetic algorithm is then employed to find the optimal parameter set that reproduces the measured reflectance and transmittance best. Finally, the optical parameters of mouse liver tissue and human brain are determined.

4.1 Introduction

The material model in the radiative transport equation (RTE) for the near-infrared (NIR) wavelength range is characterised by four wavelength dependant parameters, namely the absorption coefficient $\mu_a$, the scattering coefficient $\mu_s$, the scattering anisotropy factor $g$ and the refractive index $n$. If the scattering phase function is not otherwise specified, it is assumed to be the Henyey-Greenstein (HG) phase function.

The ability to build and simulate increasingly complex numerical models (thanks to increasing computational power) also increases the requirements for optical properties. The higher the level of detail which is possible in the numerical models, the higher the demand for characterisation of smaller and smaller tissue structures, which gets ever more challenging. The resolution of today’s magnetic resonance imaging (MRI) systems is in the sub-millimetre range and allows for example the segmentation of individual meninges layers for the numerical model, which calls at the same time for the determination of the corresponding optical properties. Additionally, the numerical model assumes that the tissue is piecewise homogeneous, which is difficult to satisfy for certain small tissue structures.
The requirements for a suitable method to determine optical properties of a material are that the method should be able to determine parameters of small pieces of tissue and phantom materials and should not put restrictions on the material regarding the optical properties. Different techniques exist to measure one or several of these properties. If a substance is non-scattering, its absorption coefficient is most easily determined by optical spectroscopy, which measures the absorption in a certain wavelength range. This technique is useful for example to determine the absorption coefficient of non-scattering liquids such as the cerebro spinal fluid (CSF). As soon as a substance is even weakly scattering, the decrease in detected intensity cannot be clearly attributed to absorption any more and the results are therefore not meaningful any more.

Reflectance and Time-of-flight absorption spectroscopy are used to estimate the absorption and the reduced scattering coefficient of tissue (even in vivo [68]). This technique is useful to determine the coefficients of large homogeneous structures, if one is not interested in the scattering anisotropy. Since they are based on evaluation of the diffusion equation, they presume a semi-infinite medium [69] and are therefore not applicable for small structures.

The determination of the scattering phase function and of the corresponding average scattering angle is challenging, but can be done with a goniometer [70]. To obtain good results, the tissue sample should be cylindrical and ideally only produce one scattering event, i.e. it should be very thin (in the orders of tens of micrometers), hence the preparation of suitable tissue samples is difficult.

The refractive index of a tissue can be determined using ellipsometry [71]. In ellipsometry, the polarisation change of the light reflected from a sample is compared to the incident beam. The refractive index of the material can then be extracted from an appropriate material model.

Another method is offered by measuring total reflectance and transmittance from a sample by means of integrating spheres and employ an appropriate reconstruction algorithm to find the set of optical properties that can reproduce the measured reflectance and transmittance values. In this work, a double integrating sphere approach is used since it offers the most general approach to determine the optical properties in any kind of phantom material or tissue in vitro.

4.2 Integrating Spheres Measurement Setup

The determination of three optical parameters requires in principle three measured quantities, for example reflectance, transmittance and the fraction of the transmitted light which passed the sample without being scattered, called unscattered transmittance [72, 73]. The determination of the reflectance and transmittance is straight-
forward. A reliable measurement of the unscattered transmittance however is very difficult since this value is very small for most materials. If the unscattered transmittance cannot be used, the reconstruction is not unique. Hence another way has to be found to obtain a determined system. A possible solution which is followed in this work is to measure reflectance and transmittance of the same material at different thicknesses. Since this leads to an overdetermined system already for two thicknesses (two reflectance values, two transmittance values), it is even possible to fit the refractive index as a fourth parameter as well, which would otherwise not be possible.

The total reflection from a sample is the sum of the individual contributions from each angle. Instead of measuring the reflected power at every angle $\theta_i$ with a goniometer, an integrating sphere can be used. As the name says, it integrates the reflections over all spatial angles (see Figure 4.1).

![Reflectance measurement with goniometer (left) and integrating sphere (right).](image)

In principle, the same sphere can be used to measure both, reflectance and transmittance, depending on the configuration. However, the re-configuration is a tedious task that requires re-alignment and re-calibration of the setup. Two dedicated spheres are therefore used, one to measure reflectance and one to measure transmittance. Figure 4.2 illustrates the setup with the spheres mounted movably on a rail. The setup is placed inside a black box to avoid ambient stray light reaching the detectors. The complexity of the system is reduced by avoiding mutual interference between the spheres. Hence the measurements are performed in two independent consecutive steps: first, the reflectance is measured with the left sphere. Second, the total transmittance is measured with the right sphere.
Figure 4.2: Double Integrating Sphere measurement setup: the reflectance sphere and transmittance sphere are mounted on XYZ stages which themselves are mounted moveable on a rail. The sample holder can alternatively be attached to either the reflectance or transmittance sphere.

4.2.1 Sphere Theory

The spheres being used have an inner diameter of 8.4 cm (Newport, USA, 819C-SL-3.3). The choice of sphere size and port diameter is subject to a trade-off. Integrating sphere theory requires the ports to be as small as possible to minimise the error [74] whilst a large sample port improves the sensitivity (small reflectance values can be detected) and specificity (two similar reflectance values can better be distinguished).

The spheres feature four ports, an input port, a detector port, a sample port and a north pole port, which is only used for sphere characterisation. The spheres are designed to be used with a collimated input beam. The port diameters of the input and detector ports are 2.54 cm and of the sample port 3.81 cm. In order to determine the correct reflectance of a sample based on a measured intensity and the sphere theory described below, there must not be any specular reflection from the sample directly onto the detector. Therefore, and in order to ensure uniform illumination of the detector, a baffle is placed by default between these two ports (see fig. 4.3). The detector port is equipped with a calibrated silicone photodetector
for the desired NIR wavelength range of 650 nm - 950 nm.

The proprietary wall material is Spectralon which has a reflectance of > 99% in the wavelength range of interest according to manufacturer specification. The different sphere ports (input port, sample port, measurement port, north pole, see Figure 4.3) have varying reflectance values, hence the overall reflectance of the wall is non-uniform. The reflectance of the \( k \)-th port with area \( a_k \) is \( \rho_k \) (all surfaces are assumed to be perfectly diffuse reflectors). Considering a sphere with an inner radius \( R \), the total area is

\[
A_s = 4\pi R^2. \tag{4.1}
\]

The ratio of the area \( a_k \) to the area of the whole sphere \( A_s \) is \( f_k \)

\[
f_k = \frac{a_k}{A_s}
\]

For a circular port with radius \( r_k \) the spherical area \( a_k \) is given by

\[
a_k = 2\pi R \left[ R - \sqrt{R^2 - r_k^2} \right]
\]

and \( f_k \) becomes

\[
f_k = \frac{1 - \sqrt{1 - \left( \frac{r_k}{R} \right)^2}}{2}. \tag{4.2}
\]

Several subscripts and terms will be used in the following derivations and are listed here for reference.
DETERMINING OPTICAL PROPERTIES

Subscripts
- $i$ input port
- $d$ detector port
- $sa$ sample
- $w$ wall
- $S_R$ reflection standard
- $S_T$ transmission standard

Terms
- $\rho_{sa}$ the reflectance of the sample investigated ($0 \leq \rho_{sa} \leq 1$)
- $\tau_{sa}$ the transmittance of the sample investigated ($0 \leq \tau_{sa} \leq 1$)
- $\rho_w$ the reflectance of the wall material ($0 \leq \rho_w \leq 1$)
- $\bar{\rho}_{sa}$ the average wall reflectance of a sphere with $n+1$ ports (with a sample attached) (this is merely a simplification of the notation in other formulas and has no direct physical meaning)
- $\rho_{we}$ the “effective” reflectance of the wall material, taking into account any imperfections (the sphere setup will never be perfect, the better it is, the closer comes $\rho_{we}$ to $\rho_w$)
- $P_0$ laser input power [W]
- $P_{sa}$ measured power at the sphere (with a sample attached) [W]

4.2.2 Power at the Detector

The relation of the measured power at the detector port to the sample reflectance and the effective wall reflectance is assessed in the following.

If a collimated input laser beam with power $P_0$ is directed on the sample, the total power in the sphere after the first reflection from the sample is [75]

$$P_{\text{tot1}} = \rho_{sa} \cdot P_0,$$  (4.3)

where $\rho_{sa}$ denotes the reflectance from the sample. The diffusely reflected light is partly reflected by the sphere ports and the sphere wall and hence the total power in the sphere after the second reflection is

$$P_{\text{tot2}} = \rho_{sa} \cdot P_0 \cdot \left( \sum_k f_k \cdot \rho_k + (1 - \sum_k f_k) \cdot \rho_{we} \right) \bar{\rho}_{sa} \quad k \in \{\text{input, detector, sample} \}$$  (4.4)
where the effective wall reflectance $\rho_{we}$ has to be determined experimentally (see next section). The average wall reflectance $\bar{\rho}_{sa}$ is introduced to simplify notation. Note that this value is a function of the reflectance of the material at the output port (either sample $\rho_{sa}$ or reflectance standard $\rho_{SR}$) since the laser beam hits this part first.

After an infinite number of reflections, the total power in the sphere is

$$P_{\text{tot},\infty} = \frac{\rho_{sa} \cdot P_0}{1 - \rho_{sa}}$$

(4.5)

and the reflected power from the sample $P_{sa}$ measured at the detector port is

$$P_{sa} = f_d \cdot P_{\text{tot},\infty} = \frac{f_d \cdot \rho_{sa} \cdot P_0}{1 - \rho_{sa}}.$$  

(4.6)

In order to calculate the sample reflectance $\rho_{sa}$, two quantities have to be determined first, the effective wall reflectance $\rho_{we}$ and the input power $P_0$.

**Effective Wall Reflectance $\rho_{we}$**

A perfect integrating sphere would have a completely Lambertian surface with a reflection of 100% over the whole wavelength spectrum and over the whole sphere area. The reflection of both the ideally very small detector and the input port would be 0% and there would be no other losses.

To characterise a real sphere including imperfections, one has to determine the effective wall reflectance $\rho_{we}$ [75]. The closer this values gets to 1, the better the setup, since the light-loss is minimised.

Two measurements with known reflectance values at the sample port need to be performed to be able to calculate $\rho_{we}$. The first one can be performed with an open sample port (Figure 4.4a), the second one in principle with a closed sample port (Figure 4.4b). Since the sphere will be used with samples mounted on the sample holder, this measurement has to be performed with a reflection standard $S_R$ mounted on the sample port instead (Figure 4.4c). The sphere is illuminated with a collimated beam with power $P_0$ from the north pole to have a diffuse illumination of the whole sphere and the sample port.

The measured power reflected from the standard is given by

$$P_{SR} = \frac{f_d \rho_w}{1 - \rho_{we} \cdot (1 - f_i - f_d - f_{sa}) - f_i \cdot \rho_i - f_d \cdot \rho_d - f_{sa} \cdot \rho_{SR}} P_0$$

(4.7)

and the measured power with open port is

$$P_o = \frac{f_d \rho_w}{1 - \rho_{we} \cdot (1 - f_i - f_d - f_{sa}) - f_i \cdot \rho_i - f_d \cdot \rho_d} P_0$$

(4.8)
Figure 4.4: Measurement procedure to determine the wall reflectance \( \rho_w \) (side view).

If we take the ratio of (4.7) and (4.8) and solve for \( \rho_{we} \) we get

\[
\rho_{we} = \frac{\left(1 - \frac{P_{SR}}{P_o}\right) \left(1 - f_i \rho_i - f_d \rho_d\right) + \frac{P_{SR}}{P_o} f_{sa} \rho_{SR}}{\left(1 - \frac{P_{SR}}{P_o}\right) \left(1 - f_i - f_d - f_{sa}\right)}
\]

(4.9)

A small uncertainty remains as reflection values for the input and detector port are unknown. However, changes in these parameters have only very little influence on \( \rho_{we} \), since their area is small compared to the overall sphere area. In this work, the following values have proven good approximations: 0.8 for the input port with custom port plug, 0.1 for the detector port.

4.2.3 Sphere Adaptations

The effective wall reflectance \( \rho_{we} \) accounts for any imperfections of the setup. Ideally, this value should be close or equal to the wall reflectance \( \rho_w \) of the sphere material. For the spheres being used, the wall reflectance is specified as > 99% by the manufacturer. The first measurements with a reflectance standard of 99% gave fairly poor results for \( \rho_{we} \) of about 0.85. Hence, the setup was improved. For the input port, a cylindrical port reducer made of Teflon was fabricated with an inner diameter of 5 mm, just large enough not to interact with the input laser beam. For the output port, three cylindrical port reducers also made of Teflon were fabricated. One with an inner diameter of 2.54 cm (Figure 4.5a), and one with an inner diameter of 1.27 cm (Figure 4.5b). A third one has also an inner diameter of 1.27 cm but has a wall bevelled towards the sphere. With this port reducer, values for \( \rho_{we} \) larger than 0.99 were obtained. This means minimal light loss inside the sphere and therefore an increased sensitivity. This is important in the reflection sphere for materials exhibiting a low reflectance which often is due to low scattering inside the sample. A high
sensitivity is also important in the transmission sphere for highly absorbing samples that exhibit very low total transmission, specially for thicker samples. An overview of the measured values is listed in table 4.1. The final setup with the added parts

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Effective wall reflectance $\rho_w$</th>
<th>Figure ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.81 cm port, 99% refl. std</td>
<td>0.853 ± 0.003</td>
<td>4.4c</td>
</tr>
<tr>
<td>2.54 cm port, 99% refl. std</td>
<td>0.924 ± 0.006</td>
<td>4.5a</td>
</tr>
<tr>
<td>1.27 cm port, 99% refl. std</td>
<td>0.949 ± 0.001</td>
<td>4.5b</td>
</tr>
<tr>
<td>1.27 cm bevelled port, 99% refl. std</td>
<td>0.995 ± 0.003</td>
<td>4.5c</td>
</tr>
</tbody>
</table>

Table 4.1: Different configuration of the sphere sample port plug and the corresponding effective wall reflectance.

Figure 4.6: Integrating sphere with custom additions and improvements: input port plug, sample port plug and sample holder (top view).
DETERMINING OPTICAL PROPERTIES

as it is used for all subsequent measurements is illustrated in Figure 4.6.

**Influence of Intensity and Wavelength on $\rho_{we}$**

In order to reduce the calibration effort that needs to be performed for every measurement, the wavelength dependence of $\rho_{we}$ has to be known. Additionally it should be independent of the input power $P_0$.

![Graph showing effective wall reflectance for different wavelengths and input powers.](image)

(a) Effective wall reflectance reflection sphere

(b) Effective wall reflectance transmission sphere

Figure 4.7: Effective wall reflectance $\rho_{we}$ for different input powers $P_0$

Figure 4.7 shows the the effective wall reflectance for the two spheres for different input powers. $\rho_{we}$ is independent of the input power $P_0$ for all port plug types and is higher than 99% for the bevelled port reducer.

Figure 4.8 shows the effective wall reflectance for five different wavelengths in the NIR range. $\rho_{we}$ shows a strong wavelength dependence for the unmodified sphere, whereas it is constant and larger than 99% for the bevelled port reducer.

The optimised spheres have a very high effective wall reflectance which is higher than 99% for all wavelengths. It is furthermore independent of the input power $P_0$. These two factors are important for the further measurements because this means that $\rho_{we}$ has to be determined only once and the same value can then be used for all of the following measurements.
4.2.4 Calibration

Due to multiple internal reflections and sphere imperfections, integrating sphere measurements tend to underestimate the reflectance and overestimate the transmittance \([74, 73, 75]\). The reflectance is underestimated, because a part of the light in the sphere is always lost through the sample if its reflectance is less than \(100\%\). The transmittance is overestimated, because a part of the light is always reflected back from the sample, whereas the calibration is performed with an open port (no reflection). The extent of under- and overestimation depends on the exact configuration of the sphere and the sample itself. A careful sphere calibration with reflection and transmission standards is therefore necessary.

From the detected power \(P_s\) in (4.6), the sample reflectance \(\rho_{sa}\) could be calculated if the input power \(P_0\) was known. The input power can be obtained from calibration measurement with a reflection standard \(S_R\) with known reflectance \(\rho_{SR}\)

\[ P_0 = P_{SR} \frac{1 - \rho_{SR}}{f_d \cdot \rho_{SR}} \]  

(4.10)

where \(P_{SR}\) is the measured power reflected from the reflection standard. Inserting (4.10) into equation (4.6) and solving for the sample reflectance \(\rho_{sa}\) yields

\[ \rho_{sa} = \left[ 1 - \rho_{we} \left(1 - \sum_k f_k \right) - f_i \cdot \rho_i - f_d \cdot \rho_d \right] \cdot \left[ \frac{P_{SR} \left(1 - \rho_{SR}\right)}{P_{sa} \cdot \rho_{SR}} + f_{sa} \right]^{-1} \]  

(4.11)

where \(S_R\) denotes the values for the reflection standard.

The theoretically predicted characteristic (4.11) of the sphere setup can be accurately reproduced by measurements with reflection standards. Four diffuse reflectance standards with reflectance values of 99%, 75%, 50% and 2%, respectively,
are used (Labsphere, North Sutton, USA: RSS-04-010). Figure 4.9 shows the curve of the sphere theory along with measurements from the calibration standards. The “true” value of the reflection standards corresponds to \( \rho_{SR} \) whereas \( R = \frac{P_{SR}}{P_{99\%}} \) denotes the raw, uncorrected reflectance value referenced to the reflected power with 99\% reflectance standard.

A similar expression for the correct transmittance value can be derived. \( S_T \) shall denote values for the transmission standard. The correct transmittance of a sample \( \tau_{sa} \) is given by

\[
\tau_{sa} = \frac{P_{sa} \cdot (1 - \rho_{Tsa}) \cdot \tau_{SR}}{P_{SR} \cdot (1 - \rho_{SR})} \tag{4.12}
\]

where \( \tau_{SR} \) is the transmittance of the reference standard and the average wall reflectance \( \rho_{Tsa} \) for the transmittance sphere is

\[
\rho_{Tsa} = \rho_{ws}(1 - f_d - f_{sa}) + f_d \rho_d + f_{sa} \rho_{sa} \tag{4.13}
\]

Note that in order to calculate the corrected transmittance of a sample, its true reflectance value \( \rho_{sa} \) has to be known or determined in advance.

The theoretical predictions are verified with neutral density filters (Thorlabs, Newton, USA: NE2R01B, NE2R04B, NE2R10B) with transmittance values of 10\%, 40\%
and 79%, respectively. The value for 100% transmittance is obtained by leaving the port open (port reducer and sample holder mounted). Figure 4.9 shows the curves obtained by the sphere theory and the measurements using the reflection and transmission standards, respectively. A very good agreement is obtained and hence a single calibration measurement is sufficient for a new wavelength or power level.

To summarise, the following steps have to be performed to obtain the reflectance $\rho_{sa}$ and transmittance $\tau_{sa}$ from a sample:

1. the effective wall reflectance of the spheres has to be determined (this step is only required once for every wavelength if the setup is not changed)
2. reflected power $P_{sa}$ from a reflectance standard and transmitted power through a transmittance standard has to be determined
3. reflected and transmitted power $P_{sa}$ from the sample have to be determined
4. reflectance and transmittance of the sample have to be calculated according to (4.11) and (4.12).

### 4.3 Parameter Reconstruction

The reconstruction of the optical properties $\mu_a$, $\mu_s$, $g$, and $n$ from measured reflectance and transmittance measurements can not be done directly since there is no algorithm $f$ to solve the inverse Problem

\[
\tilde{f}(\rho_{sa}, \tau_{sa}) \not\rightarrow \mu_a, \mu_s, g, n. \quad (4.14)
\]

Only the forward problem

\[
f(\mu_a, \mu_s, g, n) \rightarrow \rho_{sa}, \tau_{sa} \quad (4.15)
\]

can be solved numerically as described in Chapter 2. The inverse problem can be tackled by combining a forward solver with a search heuristic to find the optimal set of parameters that reproduces the measured reflectance and transmittance values.

The reconstruction of the optical parameters from the measurement values happens in three steps. First, a Monte-Carlo (MC) model is constructed to solve the forward problem, i.e. to obtain reflectance and transmittance values of a sample for a given set of optical parameters. The forward problem is solved for a large number of parameter combinations ($> 3'300$), serving as a lookup table for the optimum search. In a second step, the optimal parameter combination is searched using a genetic algorithm (GA). The fitness of a certain parameter combination is hereby determined by comparing the measured reflectance and transmittance values to the (interpolated) values from the lookup table. Finally, the reflectance and transmittance values corresponding to the optimal parameter set are compared to the measured values and
to the results from another MC simulation for the particular parameter set to prove that the interpolation provides accurate values.

The often used inverse adding-doubling [76] procedure combines the Adding-Doubling (AD) forward solver with a gradient based minimum search algorithm. The AD cannot account for losses which might occur at the transition between sample and port, e.g., in the case of thick or highly scattering samples as shown in Figure 4.10. As will be shown in the following, the fitness landscape shows multiple local minima, hence the results of the gradient based minimum search depend on the chosen initial value and may not lead to the global optimum.

### 4.3.1 Monte-Carlo Model

A Monte-Carlo model as described in section 4.3.1 will be used for solving the forward problem. A large sample thickness can lead to considerable spreading of the incident beam for strongly scattering materials as illustrated in Figure 4.10. Potentially, a part of the light could be absorbed by the sample holder or scattered away. Figure 4.10 illustrates the setup for the MC simulation, including a source modelling a Gaussian beam with beam waist $w_l = 1\, \text{mm}$, the sample of varying thickness $d \in (0.5, 1, 2, 4)\, \text{mm}$ and a port of the sphere. The Monte Carlo model counts the photon weights detected by the circular port opening. This forward problem is simulated for a large number of parameter combinations $0.001 \leq \mu_a \leq 1.0$, $0.1 \leq \mu_s \leq 50.0$, $0.0 \leq g \leq 1.0$, $1.3 \leq n \leq 1.7$ and the variable thickness $d$. These simulation results yield two five-dimensional matrices for $\rho_{sa}$ and $\tau_{sa}$. The values between the simulated points are interpolated using second order splines. Figure 4.11 shows the reflectance

![Figure 4.10](image-url)
Figure 4.11: Reflectance and transmittance values of the interpolation matrix for \( d = 2, g = 0.5, n = 1.5 \). Red dots indicate parameter combinations, for which an MC simulation was run to obtain reflectance and transmittance values. The remaining values are interpolated using second order splines.

and transmittance values for the model case where \( d = 2, g = 0.5 \) and \( n = 1.5 \). The results for parameters for which an MC simulation was run are marked with red dots, the intermediate points are interpolated.

### 4.3.2 Optimum Search

In order to find the set of optical parameters \( \mu_a, \mu_s, g \) and \( n \) that produces reflectance and transmittance values \( \rho_{sa} \) and \( \tau_{sa} \) that are closest to the measured ones, a search algorithm is needed that evaluates the quality (or fitness) of a particular solution. It also gives suggestions in which direction to look for the next, presumably better solution. The choice of an optimal search algorithm depends largely on the situation.

The measurement values, which are corrected as described in section 4.2.4, are compared with the solutions stored in the MC-lookup table. Depending on the previous knowledge of the properties of the sample, one or more parameters can be narrowed down in the search space. For example the refractive index is known for silicone phantom materials and will be fixed at the corresponding value for the reconstruction. The fitness of a particular set \( \mathcal{P} = [\mu_a, \mu_s, g, n] \) is determined by the relative error \( \mathcal{E} \) between the measured reflectance \( \rho_{sa} \) and transmittance \( \tau_{sa} \) and the interpolated simulated reflectance \( R_{GA} \) and transmittance \( T_{GA} \) corresponding to this parameter set, respectively. The error is determined over all measurements of a particular material in the different thicknesses available and is calculated as follows.
\[
\mathcal{E} = \frac{\sum_{d \in \{0.5, 1, 2, 4\}} (\rho_{sa}^d - R_{GA}^d)^2 + (\tau_{sa}^d - T_{GA}^d)^2}{\sum_{d \in \{0.5, 1, 2, 4\}} R_{GA}^d + T_{GA}^d^2},
\]

where lower error means higher fitness.

The exact shape and nature of the fitness landscape is unknown and may be different for every sample. Hints on the shape of the fitness landscape of a specific sample can be obtained by calculating the fitness values for a number of different parameter combinations \(\mu_a, \mu_s, g\) and \(n\). Figure 4.12 shows the fitness values calculated for

\[
\begin{align*}
g &= 0.0 & g &= 0.5 \\
g &= 0.9 & g &= 0.99
\end{align*}
\]

Figure 4.12: Fitness Landscape for one mixture and the two parameters \(\mu_a\) and \(\mu_s\) for four different values of \(g\). The fitness, corresponding to the inverse error, is plotted in logarithmic scale.
a number of different parameter combinations (at a fixed refractive index) from a specific phantom sample. Other visualisations have shown that there exists multiple local minima.

Therefore, an appropriate search strategy should be able to find the optimal solution by preferably putting little restrictions on the shape of the fitness landscape. Optimisation strategies that could potentially be employed are for example the downhill simplex method (Nelder-Mead) with random restart or evolutionary strategies. Reproducible and accurate results for the optimal parameters set $P_{\text{opt}} = [\mu_a^{\text{opt}}, \mu_s^{\text{opt}}, g^{\text{opt}}, n^{\text{opt}}]$ were obtained with a genetic algorithm. The details of the GA are described in Appendix C.

4.3.3 Reconstructed Parameters

The quality of the reconstruction and the expected error are assessed in the following. The reflectance and transmittance ($\rho_{sa}, \tau_{sa}$) of a purely scattering silicone phantom (manufactured with 100 ml silicone and 0.1 g TiO$_2$) in four thicknesses are determined as described above. These values are then compared with the reflectance ($R_{GA}$) and transmittance ($T_{GA}$) values corresponding to the parameters found by the GA. Figure 4.13 shows the interpolated reflectance and transmittance values of

![Figure 4.13: Reflectance and transmittance for the optimal parameter set $P_{\text{opt}}$ found by the genetic algorithm (•--•). -○- shows the relative error compared to the measurement.](image)

one specific sample. The optimal set of parameters found for this sample is $P_{\text{opt}}$: 
\( \mu_a = 0.0 \text{ mm}^{-1}, \mu_s = 2.72 \text{ mm}^{-1}, g = 0.46 \) and \( n = 1.42 \). The relative error of these reflectance and transmittance values is compared with the corrected measurement. The reconstruction algorithm is able to find an optimal parameter set whose reflectance and transmittance values match the measured values very precisely.

The GA operates with a lookup table of precomputed reflectance and transmittance values and interpolates in between if necessary. The quality of the interpolation is determined by comparing the interpolated reflectance and transmittance values with results from another MC simulation (\( R_{MC}, T_{MC} \)) performed with the parameter set \( P_{opt} \) found by the GA. Figure 4.14 shows the relative error between the reflectance and transmittance values interpolated from the lookup table and values calculated in an extra MC simulation with \( P_{opt} \). The interpolation from a set of precomputed reflectance and transmittance values is accurate with an error below 8%.

### 4.4 Optical Properties of Tissue

The list of values for optical properties of tissue published in literature are not available for the whole NIR spectrum. On top of that, the available values vary considerably, depending on the author and the measurement technique used to determine the values. The found variations can be as much as an order of magnitude. A first review of optical properties which is often used in studies and comprises optical properties of various tissues from different animals as well as of human tissues was compiled by Cheong et al.[77] and a more recent review has been done by Madsen et al. in 2012 [78].

The lack of optical properties for certain wavelengths and the uncertainty in available parameters has led to the development of the setup mentioned above and to the following tissue measurements.

In this work, the optical parameters of two types of tissue are determined: mouse liver tissue and human brain tissue. The mouse tissue samples have been provided...
by the animal imaging centre (AIC) of the Laboratory of Biomedical Engineering of ETH Zurich. The human brain tissue was provided by the University Hospital of Zurich.

4.4.1 Mouse Liver Tissue

A first experiment was performed with mouse liver tissue. The impact of time on tissue characteristics is hereby explicitly analysed.

Preparation of the Mouse Liver

The mouse was perfused before extraction of the liver in order to reduce (the highly absorbing) blood content of the liver. It is assumed that in vivo properties can be obtained by creating an effective material combined from liver tissue values and pure blood values.

Four good samples could be extracted from one mouse liver. The tissue slices were then placed in a silicon O-ring (see Figure 4.15a) with an inner diameter of 10 mm and thickness of 1 mm and 2 mm, respectively. It is important that the tissue fills out the whole ring, avoiding any holes, air bubbles or the like. The O-ring is covered with round glass cover slips on either side and mounted between two plastic frames, holding everything together firmly tight (see Figure 4.15a).

A visual inspection (see Figure 4.15b) shows that the liver samples are very homogeneous. It was difficult to attain a uniform thickness of the samples because of...
the elastic nature of the tissue. The tissue was slightly squeezed between the glass cover plates.

It has been shown [79] that the optical properties show a strong temperature dependence above a certain level due to tissue degradation (coagulation). Hence in order to minimise the degradation of the tissue, the samples have been thoroughly cooled with ice from extraction of the mouse throughout the whole experiment (except when placed between the spheres for measuring).

**Measurements**

The first measurement was conducted one hour after tissue extraction. Measurements were performed over the course of eight hours. The measurement plots are annotated with the relative time after the tissue extraction. All measurements were done at 670 nm. The samples were kept in ice during the whole measurement period, except for a last measurement which was performed 24 hours after tissue extraction. For the last 16 hours the tissue was not cooled any more to study the influence on tissue degradation.

**Results**

The reflectance from all samples was very low (Figure 4.16). The values for the 1 mm samples and the 2 mm samples were only clearly separated after the first hour and somewhat stable between three to seven hours after tissue extraction. A large change in the reflectivity is not noticeable. Only when the tissue is not kept on ice any more, the reflectivity goes slightly down.

The total transmittances (Figure 4.17) for the 1 mm samples and the 2 mm samples are clearly separated. They are furthermore very stable over the whole measurement period. Again, when the tissue remains uncooled, the properties change, leading to an increased transmittance. Cooling down the tissue to a few degrees above zero sufficiently slows down the degradation process to prevent that the optical properties are altered.

**Optical Parameter Reconstruction**

The parameters are reconstructed as described in section 4.3. The reflectance and transmittance values are averaged between two and seven hours, considering only the stable period. They are furthermore averaged over the two samples of the same thickness, leading to a reflectance value of $\rho_{1\text{mm}} = 0.0504$ and $\rho_{2\text{mm}} = 0.0638$, respectively and corresponding transmittance values of $\tau_{1\text{mm}} = 0.2250$ and $\tau_{2\text{mm}} = 0.0885$. 
Figure 4.16: Reflectance of the samples over time and without ice.

Figure 4.17: Transmittance of the samples over time.

Figure 4.18 shows the reflectance and transmittance obtained from the reconstructed parameters $\mu_a = 0.41 \text{ mm}^{-1}$, $\mu_s = 15.02 \text{ mm}^{-1}$, $g = 0.864$. The relative error compared to the measurement is plotted above.

The reconstructed parameters for the mouse liver agree with published values. The relative error for the reflectance and transmittance values is very low except for the transmission measurement for the 2 mm sample where it is almost 30%. Table 4.2 shows published values for optical properties of rat liver along with the results from the parameter reconstruction of this work. No published values for mouse liver
4.4.2 Human Brain Tissue

For NIRS measurements, it is paramount to have accurate optical parameters of human brain tissue at the desired wavelengths. Optical properties have been determined \textit{in vitro} by van der Zee [82], Beek [83], Yaroslavsky [84] and Gebhart [85], \textit{in vivo} by Bevilacqua [86]. These values show large discrepancies (see Figure 4.19). In order to be able to classify these values, the optical properties of brain tissue are measured in this work as well. The values are measured in \textit{in vitro}.
Preparation of the Tissue

Thanks to the University Hospital Zurich it was possible to obtain a $2 \times 1 \times 0.5$ cm slice of human brain. The brain was fixated and stored in formol at the time of measurement for two weeks. From the larger piece, smaller, 1 and 2 mm thick slices were cut to fit in sample holder described in section 4.4.1. Two samples of each thickness could be prepared, mostly consisting of white matter.

Measurements

The measurements were successively performed at 5 discrete wavelengths in the NIR region: 670 nm, 785 nm, 808 nm, 852 nm and 915 nm.

Results

The parameters are reconstructed for each wavelength separately as described in section 4.3. The refractive index is fixed at $n = 1.38$, corresponding to the average value of all wavelengths obtained in a first run of the reconstruction. The reconstruction is run 20 times and a mean and standard deviation is calculated. The relative error of the reflectance and transmittance values compared to the measured ones was below 0.1% for all reconstruction runs. The error bars in Figure 4.19 denote the range, for which the corresponding reflectance and transmittance values are still below a relative error of 0.1% (as calculated by (4.16)). It was abstained from creating a linear fit since the exact wavelength dependence is unknown and may not be linear. Figure 4.19 shows the values of the reconstruction along with values available in literature: Yaroslavsky [84], Beek [83] and Gebhart [85]. The absorption coefficient is higher than in the other publications, the scattering coefficient $\mu_s$ is in the same range but the scattering anisotropy is slightly lower, resulting in a slightly higher reduced scattering coefficient $\mu_s'$. However, the trend for an increasing absorption coefficient and a decreasing reduced scattering coefficient for longer wavelengths is confirmed.

Many factors may explain the variations. Differences to the values from Yaroslavsky [84] are for example: Yaroslavsky et al. measured non-fixated tissue 48 hours after extraction. The tissue in this work was fixated in formol for two weeks. The fixation may slow down but not prevent tissue degradation, hence the parameters may be different for freshly extracted tissue. A second difference is that Yaroslavsky et al. measured cryosectioned samples with a thickness of around 200 µm and washed the samples to remove all the haemoglobin, whereas the samples in this work had a thickness of 1 mm and 2 mm and the haemoglobin was not removed. This may explain the higher absorption coefficient obtained in this work.
Figure 4.19: Comparison of *in vitro* optical properties of white matter from different publications.

The values cannot reduce the variation in the parameters found in other publications. This confirms the challenging task of determining universally valid optical properties of tissues. It means at the same time that published values should be used with the necessary caution.

4.5 Summary

This chapter has introduced the necessary parts to be able to determine the optical parameters $\mu_a$, $\mu_s$, $g$ and also the refractive index $n$ from tissue and phantom ma-
Determination of optical properties. The ready-made integrating spheres were improved with custom made parts yielding an almost perfect effective wall reflectance of 0.99 and improving the sensitivity for low reflectance and transmittance values. The measurement of the same sample at different thicknesses results in a determined (or overdetermined) system that allows one to fit the optical parameters including the refractive index, which is not possible otherwise. The parameter fitting is performed by combining a forward model that calculates reflectance and transmittance values from a given set of parameters and a search algorithm that finds the optimal parameter set. Reflectance and transmittance values are obtained with an accurate Monte-Carlo model, which accounts for the light losses on the side of the sample and between the sample and the sphere and is therefore favourable over the Adding-Doubling method. The fitness landscape of the search space contains local minima which are tackled with a genetic algorithm to find the optimal parameter set. In this way, the optical parameters of mouse liver tissue and human brain were determined. The results are in the (wide) range of published values and confirm the challenges in obtaining universally valid parameters for tissue.
5 Numerical Studies

Abstract — The unique possibility of numerical studies to analyse a certain aspect in an isolated and if necessary simplified setup makes it an indispensable tool for development and improvement of biomedical applications. This chapter presents a number of numerical studies performed with the photoncruncher described previously. A layered head model is introduced as a versatile structure to analyse different aspects that are important in near-infrared spectroscopy measurements. Sensitivity analyses of the absorption coefficient of various layers show that the extra cerebral contamination of the signal may render it useless to detect changes in the white matter. The penetration depth of photons is assessed for different detector distances from the source. Simulation results from a realistic head model are compared to results obtained from a layered model showing the influence of the complex structure on the light propagation.

5.1 Introduction

Numerical studies offer the possibility to analyse a certain aspect of a complex problem in an isolated and if needed simplified setup. This is specially useful in biomedical applications, where most parameters of the system can not be altered at all or only in a very limited range. For example the oxygen saturation in blood can only be varied in a very small range when considering near-infrared spectroscopy (NIRS) measurements on humans. These limitations are lifted in numerical studies performed in this chapter.

The first example shown in section 5.2 is a thought experiment that led to the development of the new fluence rate calculation method described in section 3.3. A second example illustrates the challenges of fluorescence molecular tomography (FMT), where the location of a fluorophore (acting as a source) has to be determined based on the intensity distribution on the surface of the object. The diffusion based model that is currently used to reconstruct the position [19] already yields impressive results. They could potentially be further improved by applying more accurate algorithms as in the example. The third series of studies concerns NIRS measurements. The influence of different parameters such as optical properties, numerical source aperture or structural dimensions on the light propagation in multi-layered
structures are assessed with simulations. Finally, the differences between results obtained from a realistic head model and results obtained from layered structures are evaluated.

5.2 Fluence in Vacuum

The first example is motivated by a thought experiment: *What happens when a single photon is launched in an evacuated sphere with perfectly white walls*? The photon will bounce around in the sphere forever since it cannot be absorbed, neither in vacuum nor by the walls. Hence the fluence rate should eventually become homogeneously distributed in the sphere.

Obviously this problem cannot be tackled with the commonly used approach to calculate the fluence rate from absorbed photon power. Even though this example is not of extremely practical relevance, it might be argued to which extent fluence rate determination via absorbed power is physically meaningful, since it does not deliver results in certain circumstances. In contrast, the novel algorithm to calculate fluence rate as described in section 3.3 can solve this problem as shown in the following. The setup is illustrated in figure 5.1. A point source is placed in the centre of the sphere with a radius of 4.5 mm (staircasing boundary). The dimensions of the grid are 10 mm $\times$ 10 mm $\times$ 10 mm with a spacing of 0.5 mm $\times$ 0.5 mm $\times$ 0.5 mm. A single photon is launched from the point source and the fluence rate is tracked in each of the voxels within the sphere.

![Figure 5.1](image-url)

Figure 5.1: The fluence rate is calculated in an evacuated sphere with perfectly white walls and a point source located in the centre. A photon launched from the source should bounce around forever and the fluence rate should eventually be homogeneously distributed in the sphere.

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$^1$white walls: total reflection but in arbitrary direction
5.3 Photon Path Length Calculation

For some applications it is of interest to know the average path length photon packets travels from the source to a certain point (usually a detector) in the computational domain. This is the case for example in NIRS to calculate blood oxygen saturation in the brain, where the differential path lengths (DPF) [8] must be known.

The DPF is a measure for the elongated path a photon packet takes in a scattering medium compared to the direct distance between a source and a detector. This has been initially introduced in transmission measurements where source and detector are opposite of each other on a common axis, but has been used for other geometries as well. However, to the knowledge of the author, DPFs have not been computed for this type of setup corresponding to a minimally invasive probe placed directly in the brain [13].

Here, DPF calculations are performed in a setup mimicking an intra-cranial probe equipped with an optical fibre placed in white matter. The tip of the probe is placed
in the centre of a block with 4 cm edge length. The probe geometry is square in cross section and has an edge length of 1.5 mm. Two detectors with area of 0.6 mm$^2$ each (active area 1.2 mm$^2$) are placed 5 mm from the end of the tip (measured from the centre of the detector). The source is placed in the centre of the probe tip and has a numerical aperture (NA) of 0.37. The block is filled with a homogeneous material that resembles white matter. The optical parameters for the four wavelengths 785, 808, 852 and 915 nm are taken from [1]

<table>
<thead>
<tr>
<th>$\lambda$ (nm)</th>
<th>$\mu_a$ [mm$^{-1}$]</th>
<th>$\mu_s$ [mm$^{-1}$]</th>
<th>$g$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>785</td>
<td>0.003</td>
<td>54.0</td>
<td>0.84</td>
<td>1.35</td>
</tr>
<tr>
<td>808</td>
<td>0.003</td>
<td>55.0</td>
<td>0.85</td>
<td>1.35</td>
</tr>
<tr>
<td>852</td>
<td>0.005</td>
<td>57.5</td>
<td>0.86</td>
<td>1.35</td>
</tr>
<tr>
<td>915</td>
<td>0.011</td>
<td>61.5</td>
<td>0.88</td>
<td>1.35</td>
</tr>
</tbody>
</table>

Table 5.1: Optical properties for white matter[1] for different wavelengths.

The value for the DPF is obtained by summing up all the individual steps $s_{ni}$ of a photon packet $p_n$ that is detected at one of the two detectors. This sum is weighted with the remaining weight of the photon packet at the detector $w_n$. A mean value is then obtained by dividing this sum by the total detected weight of the detector $w_{tot} = \sum_n w_n$. This value is finally divided by the distance $d$ between the tip of the probe and the centre of the detector (5 mm in this case) to obtain the DPF value

$$\text{DPF} = \frac{\sum_n (w_n \sum_i s_{ni})}{\sum_n w_n} \cdot \frac{1}{d}. \quad (5.1)$$
The DPFs obtained for this setting are listed in Table 5.2. The differential path length factor is largest for the shorter wavelengths, hence it is assumed that photons with a shorter wavelength travel a longer path from the source to the detector on average. This somewhat counter-intuitive, since one might expect a shorter path length if the photon is scattered less. The absorption coefficient and scattering coefficient are however highest for 915 nm but the DPF for this wavelength is the smallest. A possible explanation is the following. Due to the high scattering coefficient, a part of the photons is very quickly diverted into the direction of the detector. The remaining photons that would require a longer way to reach the detector are absorbed due to the higher absorption coefficient.

The values obtained in these simulations are much higher than the values reported in literature [87, 88], although the same wavelength dependence is obtained. As expected, the differential path length is very much dependent on the exact geometrical configuration of the source and the detectors and on the optical parameters employed. Therefore one has to be very careful when adopting DPF values from literature.

### 5.4 Fluorescence Molecular Tomography

The full capabilities of the photoncruncher are exploited when using complex anatomical structures as input geometries. Such structures can be constructed based on segmented MRI (magnetic resonance imaging), CT (computed tomography) or PET (positron emission tomography) images. High resolution data sets are publicly available for a mouse, known as Digimouse [89]. The dataset is constructed from registered images obtained by PET, CT and cryo-section. The resolution of the dataset is 0.1 mm × 0.1 mm × 0.1 mm. The model contains 21 different structures. The optical properties are taken from [90] and [77].

Fluorophores can be tailored to bind to certain macromolecules which in turn are used as tracers for a specific tissue, e.g. cancer tissue. Hence if the source of a fluorophore can be localised by optical means (called Fluorescence Molecular
Tomography, FMT), the tissue it binds to is localised as well. To study the effect of a fluorescent substance concentrated at one point in the brain, an isotropic point source is used. Figure 5.4 shows the fluence rate (in units [W mm\(^{-2}\)]) on the surface of the brain and on the surface of the skin. Since the source is buried in the brain, the light is already very dispersed on the surface of the brain and even more on the outer surface of the mouse. This illustrates the challenges and complexity of the reconstruction of fluorophore positions from FMT images [19].

**5.5 Near-Infrared Spectroscopy**

Light propagating from a source on the skin through the superficial layers down to the brain and back to a detector on the skin is considerably influenced by the different tissue layers. Therefore, the reconstruction algorithms for non-invasive NIRS applications need to take into account the influence of the head structure on the light propagation.

The layered geometry has been found to be a versatile structure to analyse different aspects in multi-material three-dimensional (3-D) geometries. The geometry presented in the following is designed to simplify and approximate a human head. It consists of five different layers: skin, skull, cerebro spinal fluid (CSF), grey matter and white matter. The employed thicknesses and optical properties are summarised in Table 5.3.

Figure 5.5 shows the general setup of the layered geometry. The computational domain is a square block with 12 cm edge length and 5 cm total thickness. The simulation setup consists of a point source which is placed on the surface of the skin.

![Figure 5.4: Fluence rate (in W mm\(^{-2}\)) on the surface of the skin (left) and the brain (right).](image)

![Figure 5.5: General setup of the layered geometry.](image)
Table 5.3: Properties of the different materials constituting the layered geometry.

<table>
<thead>
<tr>
<th>type</th>
<th>thickness</th>
<th>$\mu_a$ [mm$^{-1}$]</th>
<th>$\mu_s$ [mm$^{-1}$]</th>
<th>$g$</th>
<th>$n$</th>
<th>source</th>
</tr>
</thead>
<tbody>
<tr>
<td>skin</td>
<td>2 mm</td>
<td>0.015</td>
<td>18</td>
<td>0.9</td>
<td>1.41</td>
<td>[91, 92]</td>
</tr>
<tr>
<td>skull</td>
<td>5 mm</td>
<td>0.025</td>
<td>28</td>
<td>0.92</td>
<td>1.56</td>
<td>[93, 94]</td>
</tr>
<tr>
<td>CSF</td>
<td>2 mm</td>
<td>0.001</td>
<td>0.01</td>
<td>0.99</td>
<td>1.33</td>
<td>[95]</td>
</tr>
<tr>
<td>grey matter</td>
<td>5 mm</td>
<td>0.035</td>
<td>62.0</td>
<td>0.95</td>
<td>1.35</td>
<td>[82, 96]</td>
</tr>
<tr>
<td>white matter</td>
<td>36 mm</td>
<td>0.01</td>
<td>47.0</td>
<td>0.8</td>
<td>1.35</td>
<td>[82]</td>
</tr>
</tbody>
</table>

Figure 5.5: Layered head structure (simplified).
Additionally to the spatially resolved fluence rate, a detector array is placed on top to track the reflection of the structure in various distances from the source. The detectors with an area of 1 cm$^2$ are placed in a distance of 1, 2, 3, 4, 5 and 6 cm from the source. The NA of the point source is set to 0.1 by default. The detectors are perfect absorbers and accept photon packets equally from all angles. Such a setup is typical for NIRS, where brain oxygenation is monitored by a non-invasive patch, which is placed on the patients head. Commercial examples of such systems are realised for example by Casmed FORE-SIGHT$^2$ or Convidien INVOS$^3$.

5.5.1 Fluence Rate

Figure 5.6 shows the fluence in a cross section of the geometry. Despite the moderate difference in refractive indices of the CSF layer and the surrounding layers, one can observe a clear light-guiding effect of this layer. For a part of the light the CSF layer is acting like a barrier and shields the deeper brain layers from the incoming light. This can potentially deteriorate the performance of non-invasive patch measurements since a part of the light is captured in the CSF layer.

Figure 5.6: Fluence rate in a layered head geometry with point source and 6 detector patches. Despite the slightly lower refractive index (1.33) of the CSF layer compared to the surrounding tissues (1.34 for grey matter, 1.51 for skull), a light guiding effect can be observed due to the non-scattering nature of the CSF layer.

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$^2$http://www.casmed.com/foresight-tissue-oximeter
$^3$http://www.covidien.com/rms/brands/invos
Comparison with COMSOL

The fluence rate is compared to results from a finite element method (FEM) simulation performed with COMSOL. The fluence calculation in the FEM simulation is based on the photon diffusion equation described in section 2.3.2. In both simulations, Monte-Carlo (MC) and FEM, a reference source power of 1 W is chosen. The diffusion theory is not applicable for low scattering regions such as CSF and fails to calculate light propagation in head structures accurately.

Figure 5.7 shows the results from the MC and FEM simulation. The diffusion equation gives useful results in the region of the skull, but fails at the surface where the fluence is overestimated and in the CSF region, where it is underestimated. The difference in grey and white matter are due to the wrong values in the CSF region. Similar results were found in [97].

5.5.2 Signal from the White Matter

The photoncruncher has the functionality to mark photon packets, once they have penetrated into a certain material. The detectors can then be configured such that they only deal with photons having a certain material marker. This allows one to separate a part of the signal which has reached a certain tissue type from the total signal. This white matter signal is of interest in non-invasive NIRS measurements to estimate the amount of light that has reached the most important tissue region of white matter. Figure 5.8a shows the received fluence of the detector patches which
Figure 5.8: a) The results of the simulation show the decrease in fluence for the detectors further away from the source. b) The ratio of the white matter signal increases, the further away the patch-detectors are from the source and slightly decreases after 3 cm. c) The relative statistical error $E_{\phi_{\text{tot}}}$ of the total signal (---), and $E_{\phi_{\text{wm}}}$ of the signal from the white matter (•••).

rapidly decreases towards the more distant detectors. Figure 5.8b shows the ratio of the white matter signal $R_{\text{wm}}$, i.e. the ratio of photons that have actually penetrated the tissue all down to the white matter and back to the detector compared to the total received signal. It is calculated as

$$R_{\text{wm}} = \frac{\phi_{\text{tot}}}{\phi_{\text{wm}}},$$

(5.2)

where $\phi_{\text{tot}}$ is the total detected fluence and $\phi_{\text{wm}}$ is the fluence only for photon packets that have reached white matter. This ratio increases as the detectors are placed further away from the source. The share of the light being backscattered from the white matter to the total detected light can therefore be increased by placing the detectors at a minimum distance of 3 cm from the source. However, the total amount of detected light drops by a factor of $2.6 \cdot 10^{-4}$. The ratio of the white matter signal to the total signal decreases slightly after a distance of 3 cm on a very low level of less than 1% of the total detected signal.

Figure 5.8c shows the relative statistical error $E_{\phi_{\text{tot}}}$ of the total signal and $E_{\phi_{\text{wm}}}$ for the white matter signal. The error is calculated after each doubling of the number of photons as described in section 3.4. The absolute error for the white matter ratio
δR_{wm} is calculated as follows

\[ \delta R_{wm} = |R_{wm}| \sqrt{\left( \frac{\delta \phi_{wm}}{\phi_{wm}} \right)^2 + \left( \frac{\delta \phi_{tot}}{\phi_{tot}} \right)^2} \]  

(5.3)

where the absolute errors \( \delta \phi_{tot} \) and \( \delta \phi_{wm} \) are given by

\[ \delta \phi_{tot} = \mathcal{E}_{\phi_{tot}} \cdot \phi_{tot} \]  

(5.4)

\[ \delta \phi_{wm} = \mathcal{E}_{\phi_{wm}} \cdot \phi_{wm} \]  

(5.5)

The errors are also shown as error bars in Figure 5.8b. The statistical error has decreased for all detectors to below 10 percent for the simulated photon packet number \( 2.1 \times 10^9 \).

The statistical error grows exponentially with the distance of the detectors, hence also the simulation time grows exponentially, if a certain error for all detectors should be achieved. This can be seen in Figure 5.8c, where the statistical error increases for larger distances between source and detector.

### 5.5.3 Penetration Depth

In order to have a better understanding of where the detected light has travelled, the maximum penetration depth of each photon packet which is received by a detector is recorded and shown in the histograms in Figure 5.9. The largest share of the

![Figure 5.9: Histograms of the maximum penetration depth of detected photons. The strong reflection at 2 cm between the skull and the CSF layer is due to the transition to a lower refractive index of the CSF compared to the skull.](image)
signal at the detector closest to the source at 1 cm distance comes from the scalp and skull. The detector at a distance of 2 cm from the source shows the strong reflection at the material interface from skull to CSF. For the detector at 4 cm virtually all of the signal comes from the grey matter, but only a small portion from the white matter.

A signal containing information about changes in the grey and white matter region is only obtained in a certain distance from the source. Detectors that are placed close to the source (less than 2 cm) contain virtually no information from the deeper layers.

5.5.4 Sensitivity Analysis

The validity of all simulations stands or falls with the accuracy of the optical properties. Inter-individual differences of tissue parameters may have a significant effect as well. Sensitivity analysis gives useful answers to the question of the importance of a certain parameter on the total propagation characteristics. In the following, the results are shown as relative difference \( \Delta \phi_{\text{tot}} \) of the calculated fluence \( \phi_{\text{tot}} \) compared to a reference case \( \phi_{\text{ref}} \)

\[
\Delta \phi_{\text{tot}} = \frac{\phi_{\text{tot}} - \phi_{\text{ref}}}{\phi_{\text{ref}}}. \tag{5.6}
\]

The corresponding error measure \( \delta \Delta \phi_{\text{tot}} \) is calculated according to error propagation laws as follows

\[
\delta \Delta \phi_{\text{tot}} = \left| \frac{\phi_{\text{tot}} - \phi_{\text{ref}}}{\phi_{\text{ref}}} \right| \sqrt{\frac{(\delta \phi_{\text{tot}})^2 + (\delta \phi_{\text{ref}})^2}{(\phi_{\text{tot}} - \phi_{\text{ref}})^2} + \frac{(\delta \phi_{\text{ref}})^2}{\phi_{\text{ref}}^2}}, \tag{5.7}
\]

and is shown as error bars in the figures.

CSF layer

In a first example, the absorption coefficient of the CSF layer is altered. The absorption of the CSF layer is very low under normal physiological conditions but can rise dramatically in case of sub-arachnoidal bleedings. The reference value for the absorption coefficient of the CSF layer is assumed to be 0.001 mm\(^{-1}\). The total volume of the CSF layer is assumed to be 200 ml. Assuming that 1 ml of blood with an absorption coefficient of 2.0 mm\(^{-1}\) [98] is dissolved in the CSF, the absorption coefficient of the CSF layer raises to 0.011 mm\(^{-1}\). Likewise, if 10 ml are dissolved, the absorption coefficient increases to 0.101 mm\(^{-1}\). The scattering coefficient is kept constant since the reduced scattering coefficient of blood is small. Figure 5.10a shows
Figure 5.10: Influence of a change of the absorption coefficient of the CSF layer on the propagation characteristics.

The relative difference $\Delta \phi_{\text{tot}}$ of the total calculated fluence $\phi_{\text{tot}}$ with respect to the reference with $\mu_a^{\text{CSF}} = 0.001 \text{ mm}^{-1}$. The error $\delta \Delta \phi_{\text{tot}}$ is shown as error bars. Figure 5.10b shows the relative difference $\Delta \phi_{\text{wm}}$ of the white matter signal $\phi_{\text{wm}}$ compared to the reference case.

$\phi_{\text{tot}}$ drastically drops for the highest absorption value. Likewise, the part of the signal that has reached the white matter $\phi_{\text{wm}}$ is largely reduced. Even for the case where $\mu_a^{\text{CSF}} = 0.01 \text{ mm}^{-1}$ there is a change in detected fluence rate of up to 40% for the detector at 4 cm distance from the source.

**White Matter**

NIRS measurements on the head are concerned with measuring changes in oxygen concentration in the brain. A change in oxygen concentration means a change in com-
position of oxygenated and deoxygenated blood, leading to a change of the absorption coefficient (see section 1.2.1). The change in the absorption coefficient of white matter for different oxygen saturation values $SO_2$ is given in appendix E. For the following study, a reference white matter absorption coefficient of $\mu_a = 0.01 \text{ mm}^{-1}$ is assumed. This value is increased by 10%, 20% and 100%. The relative change of the total signal $\Delta \phi_{\text{tot}}$ is shown in figure 5.11a. The total signal is almost unaffected by changes in the absorption coefficient of the white matter. Small changes are visible for the white matter signal $\phi_{\text{wm}}$ as shown in figure 5.11b, although a clear trend is not apparent.

**White Matter and Skin**

In a second study, it is assumed that oxygenation changes will also affect the skin and hence change the absorption coefficient of the skin as well. The reference value for skin $\mu_a^{\text{Skin}} = 0.015 \text{ mm}^{-1}$ is therefore likewise increased by 10%, 20% and 100%. Figure 5.12a shows the relative change in calculated fluence $\Delta \phi_{\text{tot}}$ compared to the reference case. Even a moderate change of the absorption coefficient of 10% is reflected in a different fluence at the detectors. Likewise, the white matter signal $\Delta \phi_{\text{wm}}$ shows large differences, as shown in figure 5.12b. These differences are however not due to the change in the white matter itself, but due to the change in absorption in the skin.
Figure 5.12: Relative changes for different absorption coefficients of the white matter and the skin, compared to the reference where $\mu_{a}^{\text{wm}} = 0.01 \text{ mm}^{-1}$, $\mu_{a}^{\text{Skin}} = 0.015 \text{ mm}^{-1}$

**Numerical Aperture**

The NA as specified in equation 3.1 or the spread of the source beam between output of the applying device on the skin surface is not always exactly known. Hence the influence of different numerical apertures (in case of optical fibres) or more general beam spreads on the detected intensity is evaluated. The source is assumed to be directly touching the material surface. A reference simulation is performed with a small NA of 0.1. The NA is then changed to 0.2 and 0.3. Figure 5.13a shows the ratio of the signal that has travelled to the white matter and back to the detectors for different NAs of the source. The relative differences of the white matter signals compared to the reference of $\text{NA} = 0.1$ is shown in figure 5.13b. The variation is around 10%, but no clear trend is apparent, hence it may be concluded that the NA has only little influence on the propagation characteristics for strongly scattering materials.

**5.5.5 Realistic Head Model**

Important insights can be gained from the layered head structure, but probably not all effects can be explained with it. A realistic head model is therefore constructed and the intensities obtained from a detector array are compared to the values of the layered structure as shown in section 5.5.2. The structural information for the simulation is obtained from a medical image data set, in this case from MRI images.
Figure 5.13: Influence of the numerical apperture or beam spread of the source on the detected intensity.

from myself, made for this purpose.

The MRI images were taken with a 3T scanner (Philips Achieva 3T) at the MRI research centre of the Institute of Biomedical Engineer at ETH Zurich. T1-weighted and T2-weighted images were assessed with a resolution of $1 \times 1 \times 1$ mm. In order to extract the structural information from these grey-value images, they have to be segmented, meaning that every pixel gets labelled with the correct tissue at the corresponding position. The segmentation was performed semi-automated with the tools provided by the Slicer package\textsuperscript{4} [99]. The provided algorithms worked well for some structures (such as the eye for example) but the segmentation still needed a lot of manual corrections to obtain a useful structure for the MC algorithm. White and grey matter were segmented based on the T1-weighted images, which showed a good contrast between the two tissues. The other structures were segmented based on the T2-weighted images. A rendering of the segmented data is shown in Figure 5.14 showing the brain, some of the cerebral veins, the eyes and the beginning of the spinal cord. For this simulation, only the part of the volume from the eyes upwards is taken to reduce memory consumption.

The segmented dataset distinguishes the following tissue types: skin, skull, cerebrospinal fluid, grey matter and white matter, the eyes and the ventricle region. The optical properties are the same as for the layered model given in table 5.3. A point source with a numerical aperture of 0.1 is placed on the surface of the skin tissue and emits light in direction of the normal with respect to the surface at the

\textsuperscript{4}http://www.slicer.org
source position. Four square detectors with an edge length of 2.65 mm are placed in a distance of 10, 20, 30 and 40 mm from the source. An area of the head was chosen where the curvature is only small.

In order to get statistically significant results, the simulation is run for 36 hours on a Linux cluster using 128 AMD Opteron cores. Figure 5.15a shows the setup with the four detector patches and the point source (indicated with the arrow) and the surface of the white matter coloured with the fluence rate. Figure 5.15b shows the fluence rate at the four detectors. The values are plotted for the complex structure and for the layered model. While the value for the detector at 1 cm is exactly the same, the values begin to differ more and more as the detectors are moved away from the source. The curvature of the head is small in this region, but it may partly explain the differences.

Although the layered head model makes an important contribution to foster the general understanding of the mechanisms influencing light propagation in the head,
it is not sufficient to explain light propagation in the head in full detail. Certain aspects such as intra individual differences in the head structure or the influence of sulcal effacement due to brain swelling will have to be studied on realistic head models, for others, e.g. sensitivity studies, the layered model is sufficient to analyse propagation characteristics. Hence in order to develop and improve reconstruction algorithms for the derivation of the oxygen content of blood in the brain from NIRS measurements, light propagation in the head has to be simulated also based on a realistic head model.

5.6 Summary

A number of numerical studies have been performed in this chapter. The average path lengths of photons between the source and the detectors are calculated for the geometrical configuration found in the minimally invasive probe. It is shown that these values largely depend on the exact geometrical configuration and on the optical parameters used and hence cannot easily be adopted from literature. Sensitivity analyses performed on a layered head model show that small changes in absorption in the white matter are very hard to be detected at the surface already in the layered structure. The detected signal is largely influenced by the top layers. Changes of the
parameters in these layers immediately lead to large signal changes for all detectors, irrespective of the distance from the source. It is shown that detectors placed close to the source (less than 2 cm) detect almost no photons that have penetrated to the deeper layers and hence the detected signal contains almost no information from these layers. The comparison between the realistic head model and the layered structure finally shows differences in detected intensity in the two models. Realistic head models will be necessary for certain analyses, for the example the influence of sulcal effacement due to brain swelling and obviously the evaluation of intra-individual structural differences on NIRS signals.
6 Tissue Mimicking Phantoms

Abstract — This chapter attempts to fill the gap for optical reference materials with properties comparable to those of tissue. Such materials are an important tool for development and characterisation of optical diagnosis and measurement devices. Silicone rubber meets the requirement for a solid and durable phantom. TiO$_2$ and carbon black powder can be added to alter the scattering and absorption properties of the phantoms covering the range of properties found in tissues. A wavelength dependent mixture formula for these addings is developed, which enables the fabrication of a solid phantom with known optical properties. The comparison of reflectance and transmittance measurements on layered phantom structures with corresponding Monte-Carlo simulations shows a very good agreement and confirms the validity of the mixture formula.

6.1 Optical Phantoms

Performance assessment, validation and optimisation of any measurement system requires well defined metrological standards. Such standards are available for example to calibrate reflection and transmission measurements of an optical system (as used in section 4.2.4). In biomedical optics, it is necessary to have materials that mimic the properties of various tissues in the near-infrared (NIR) range (650 nm-950 nm). These tissue mimicking materials are required to represent for example optical properties such as scattering and absorption (wavelength dependent), fluorescent responses, mechanical stability or even acoustic impedances if combined applications with ultrasound are involved.

Tissue mimicking optical phantoms typically consist of a matrix material with scattering and absorbing agents added. Besides aqueous solutions, agar [100], polyurethane [101] or silicone rubber [102] have been used as base materials. Popular scattering agents specially for aqueous solutions are intralipid [103, 104] whose scattering properties are well characterised [105] or other lipids [106]. Metal oxides such as titanium dioxide (TiO$_2$) [107] and Al$_2$O$_3$ or polystyrene [108] and glass spheres [109] are mostly used for solid phantoms. Dies such as india ink [103] are often used as absorbing agents. Another interesting approach is the use of three dimensional (3-D) printing for optical phantoms [110].
The major requirements for the phantoms are mechanical stability, combinability of different mixtures representing different tissues and the ability to generate complex 3D geometries with the possibility of incorporating other tissue mimicking, or even real substances or liquids (such as blood for example). The chosen approach to achieve these requirements is to use two-compound silicone rubber based mixtures whose optical properties can be tuned by adding scattering and absorbing agents. TiO$_2$ added to silicone is able to cover the range of scattering coefficients found in tissue [107] and is used here as scattering agent. Carbon Black (CB) is used as absorption agent [111].

A consent and much less a recipe on how to create optical phantoms does not yet exist. Attempts have been made to compare optical properties from defined liquid phantom solutions between different laboratories, still showing considerable variations of more than ten percent [103]. However, standardised reference materials with defined optical properties are not available to date, mainly due to lack of official specifications how to create such materials. In order to close this gap, a mixture formula is developed in this work. It enables the manufacturing and confection of solid silicone phantoms exhibiting well-defined and reproducible optical properties. The development of the mixture formula is based on measurements with the double-integrating spheres setup (see section 4.2) and the reconstruction of optical properties exploiting Monte-Carlo (MC) simulations combined with a genetic algorithm (GA) as explained in section 4.3.1.

The question arises, how this mixing formula can be validated. Do silicone phantoms manufactured with this mixing formula achieve the optical properties they are tailored to? This validation is successfully performed by producing a multi-layered phantom with different optical properties and performing optical measurements with a laser source and photo-detectors in various positions on the layered phantoms. The same setups are numerically reproduced with MC simulations employing optical properties as determined by the mixing formula.

### 6.1.1 Silicone Phantoms

For the phantoms, a two-compound silicone rubber (Elastosil RT 601, Wacker Silicone, Munich, Germany) consisting of silicone (part A) and curing agent (part B) is used. TiO$_2$ is added as a scattering agent and carbon black (CB) as absorption agent. Both are used in powder form (Scholz-Farbpigmente, Dietikon, Switzerland), which is dissolved in the curing agent (part B) and extensively stirred with a stirrer to prevent clustering of the powder particles. The silicone (part A) is added and thoroughly mixed. The viscous compound is then poured into a mould of desired dimension and shape. A number of examples are presented in Figure 6.1, showing the versatility of shapes and optical properties which can be achieved with silicone.
phantoms: square, cylinder, spherical or cone like shapes exhibiting non-absorbing (white) to nearly perfectly absorbing (black) optical properties.

For the samples that are used to develop the mixing formula, a mould made of acrylic glass is used (see figure 6.2a). Acrylic glass exhibits an extremely smooth surface, which is required for the phantoms. A non-smooth phantom surface results in reflection artefacts which would distort the measurements of the optical properties of the bulk phantom material. The silicone-filled moulds are encapsulated in a vacuum chamber several times to prevent bubble formation. The samples are cured at room temperature and normal pressure for 24 hours. It is possible to reduce the curing time by exposing the phantom to higher temperatures, but care has to be taken because fast curing prevents the ascent of undesired air-bubbles that are inevitably introduced in the manufacturing process.

6.2 Mixture Formula

The goal is to extract a mixing formula for compounds consisting of silicone, TiO$_2$ and Carbon Black. The formula should allow the determination of the TiO$_2$ and CB concentrations required to produce a silicone phantom with certain optical parameters
TISSUE MIMICKING PHANTOMS

(a) Mould to cast thin silicone samples. (b) Slide to hold the thin silicone samples to be used with the integrating sphere setup.

Figure 6.2: Sample mould and holder.

$\mu_a$, $\mu_s$ and $g$ in the wavelength range of 650 nm-950 nm of the NIR spectrum.

6.2.1 Analytical Estimation of the Scattering Parameter

Assuming that the dispersed TiO$_2$ particles are spherical, the scattering parameter and anisotropy factor $g$ can be estimated using Mie theory [112]. Because the size of the TiO$_2$ particles is subject to a certain variation due to their manufacturing process, it is not possible to determine the exact size distribution $n(D)$ of the particles. Therefore, a log-normal distribution with a probability density function given by

$$w(D; \mu, \sigma) = \ln N(D; \mu, \sigma) = \frac{1}{D \sigma \sqrt{2\pi}} e^{-\frac{(\ln D - \mu)^2}{2\sigma^2}}, \ D > 0$$

(6.1)

with location parameter $\mu$ and scale parameter $\sigma$ is used as an approximation to model the size distribution of the TiO$_2$ particles. Figure 6.3 shows four distributions with scale parameter $\sigma = 0.2$ and different location parameters $-1.5 < \mu < 0.0$. According to manufacturer specifications, the average particle diameter can expected to be in the range 0.3 $\mu$m to 0.7 $\mu$m depending on the dispersion quality. The average particle diameter from a given distribution can be calculated by

$$\langle D \rangle = \int D \cdot w(D) \, dD.$$  

(6.2)
Figure 6.3: Possible probability density functions for TiO$_2$ particle diameter distributions. The vertical lines indicate the average diameter, according to equation 6.2.

Assuming a known TiO$_2$ concentration $c_{\text{TiO}_2}$ and silicone volume $V_{\text{sil}}$ the total TiO$_2$ mass is given by

$$M_{\text{TiO}_2} = c_{\text{TiO}_2} \cdot V_{\text{sil}} \tag{6.3}$$

and the mass of a single particle with diameter $D$ by

$$m_{\text{TiO}_2}(D) = \frac{D^3 \pi}{6} \rho_{\text{TiO}_2} \tag{6.4}$$

where $\rho_{\text{TiO}_2} = 4.23 \text{ g cm}^{-3}$ is the density of TiO$_2$. The average mass of a particle for the distribution $w(D)$ is then given by

$$\langle m_{\text{TiO}_2} \rangle = \int_0^\infty m_{\text{TiO}_2}(D) w(D)dD. \tag{6.5}$$

The total number of TiO$_2$ particles per unit volume is given by

$$\rho = \frac{c_{\text{TiO}_2}}{\langle m_{\text{TiO}_2} \rangle} = \int_0^\infty n(D)dD. \tag{6.6}$$

The Mie solution for the total scattering intensity $\sigma_s$ (scattering cross section) from a spherical particle is given in (2.31) (section 2.2.4) and is repeated here for reference

$$\sigma_{\text{sca}} = \frac{2 \pi a^2}{x^2} \sum_{n=1}^{n_{\text{max}}} (2n+1)(|a_n|^2 + |b_n|^2). \tag{6.7}$$
The evaluation of the coefficients $a_n$ and $b_n$ up to a certain $n_{\text{max}}$ contains some subtle numerical challenges. Stable and accurate results were obtained by following the algorithm described by Wang [38]. It is assumed (as for the radiative transport equation (RTE)) that each scattering event (i.e. each particle) can be treated individually and that neighbouring particles do not have an influence. A TiO$_2$ concentration of 4 g/l leads to a volume fraction of less than 0.1%. Hence this assumption seems reasonable.

The average scattering cross $\langle \sigma_{\text{sca}} \rangle$ section is given by

$$\langle \sigma_{\text{sca}} \rangle = \int \sigma_{\text{sca}}(D) \cdot w(D) \, dD,$$

which leads to an average scattering coefficient of

$$\langle \mu_s \rangle = \langle \sigma_{\text{sca}} \rangle \cdot \rho,$$

where $\rho$ is the number of particles per unit volume. Similarly, an average scattering anisotropy $\langle g \rangle$ can be calculated. The refractive index for rutile TiO$_2$ is calculated with the dispersion formula described in [113] which yields 2.49 at 670nm. Figure 6.4 shows the expected average scattering parameter $\langle \mu_s \rangle$, the reduced scattering coefficient $\langle \mu'_s \rangle = \langle \mu_s \rangle \cdot (1 - \langle g \rangle)$, and average scattering anisotropy $\langle g \rangle$ for a log-normal particle distribution with $-1.5 < \mu < 0.0$ and $\sigma = 0.2$. The TiO$_2$ concentration for this calculation is 2 g/l, the CB concentration is 0.1 g/l and the wavelength is 670 nm.
average particle size for log-normal distributions with $-1.5 < \mu < 0.0$ and $\sigma = 0.2$. The TiO$_2$ concentration for this calculation is 2 g/l, the CB concentration is 0.1 g/l and the wavelength is 670 nm. The average diameter of the particles is expected to be in the range between 0.3 $\mu$m and 0.7 $\mu$m. In this range, both the scattering coefficient $\mu_s$ and the scattering anisotropy are strongly dependent on the exact size distribution of the particles, hence slight variations in $\mu_s$ and $g$ have to be expected between different sample batches. However, the reduced scattering coefficient $\mu'_s$ is less sensitive on the exact particle size distribution.

### 6.2.2 Phantom Series

Phantoms were produced for 16 different combinations of TiO$_2$ and CB concentrations. TiO$_2$ concentrations of 0, 1, 2 and 4 g/l were used and CB concentrations of 0, 0.05, 0.1 and 0.2 g/l. From each mixture, three samples per thickness at four different thicknesses 0.5, 1, 2 and 4 mm were casted, which makes a total of 192 samples. Figure 6.5 shows the four phantoms (in different thickness) of one mixture.

![Figure 6.5: Example of a series of thin silicone samples used for measurements with the double integrating sphere system for the parameter reconstruction. The samples are made from the same mixture but with different thicknesses, hence they appear with different opacity.](image)

For each of the 12 samples per mixture, reflectance $\rho_{sa}$ and transmittance $\tau_{sa}$ are measured at five different wavelengths. The parameter reconstruction is then performed for every mixture at every wavelength as described in section 4.3. Deduced from the Mie calculations, the search space for $g$ can be restricted to the interval [0.4, 0.8]. The refractive index of silicone is fixed at 1.42 [107], hence it is assumed,
that the TiO$_2$ and CB concentration do not alter the macroscopic refractive index of silicone.

6.2.3 Parameter Reconstruction

Figure 6.6: Reconstructed optical parameters $\mu_a$ and $\mu'_s$ for the 16 mixtures for $\lambda = 670$ nm. The red line is the best linear fit with a correlation coefficient for $\mu_a$ of $R^2 = 0.976$ and for $\mu'_s$ of $R^2 = 0.992$. The fitting errors for all wavelengths are shown as error bars in figure 6.7.

Figure 6.6 shows the reconstructed parameters $\mu_a$ and $\mu'_s$ for all mixtures at a wavelength of $\lambda = 670$ nm as example. These results show a linear relationship between concentration of CB and the absorption coefficient $\mu_a$ and concentration of TiO$_2$ and the reduced scattering coefficient $\mu'_s$, respectively, as suggested from theory [32] according to (6.9). Due to the sensitivity of the scattering coefficient $\mu_s$ and the scattering anisotropy $g$ on the exact size distribution of the TiO$_2$ particles, it is appropriate to use the reduced scattering coefficient $\mu'_s$ for the derivation of the formula.

It is important to note that the scattering parameters $\mu'_s$ do not significantly depend on the concentration of absorber CB, and vice versa. This applies to the concentrations used in this study (however, an influence for higher concentrations can not be completely excluded). This is shown in figure 6.6, where the magnitude of $\mu_a$
does not significantly depend on the concentration of TiO$_2$ and vice versa. Hence the absorption coefficient can independently be controlled with the concentration of CB and the scattering coefficient can independently be controlled with the concentration of TiO$_2$.

The interaction cross sections $\sigma_{CB}$ and $\sigma_{TiO_2}$ per unit weight of CB or TiO$_2$ are obtained from the linear fits

$$\mu_a = \sigma_{CB} \cdot c_{CB}$$
$$\mu_s = \sigma_{TiO_2} \cdot c_{TiO_2}$$

(6.10)

of the results from the parameter reconstruction shown in Figure 6.6. The interaction cross sections are wavelength dependent, hence these fits have to be performed for each of the five wavelengths measured. The units of the interaction cross sections are area per weight or $1/(g \cdot \text{mm})$, depending on the unit of the concentration. The fitting error for all wavelengths is shown by error bars in Figure 6.7.

![Figure 6.7: Wavelength dependence of the interaction cross sections $\sigma_{CB}$ (■) and $\sigma_{TiO_2}$ (□) and their corresponding fits.](image)

The wavelength dependence of the interaction cross sections $\sigma_{CB}$ and $\sigma_{TiO_2}$ are shown in figure 6.7. The scattering cross section shows a slight decrease towards the longer wavelengths whereas the absorption coefficient remains almost constant over the wavelength range. The wavelength dependence of $\sigma_{CB}$ and $\sigma_{TiO_2}$ can be approximated with first and second order polynomials, respectively, as follows

$$\sigma_{CB}(\lambda) = 8.50 \times 10^{-5} \cdot \lambda + 2.11$$
$$\sigma_{TiO_2}(\lambda) = -9.77 \times 10^{-6} \cdot \lambda^2 + 1.40 \cdot \lambda - 3.80$$

(6.11)
where \( \lambda \) is in nm. The validity of these approximations has not been confirmed for the wavelengths beyond the range from 650 nm to 950 nm.

The scattering parameters obtained from the reconstruction agree with the analytical estimation in section 6.2.1, indicating an average particle diameter of 0.8 \( \mu \)m. The average particle diameter can be seen as an indicator of how good the powder is dispersed in the silicone. The average diameter is slightly above the expected range of 0.3 to 0.7 \( \mu \)m, suggesting that small clusterings of TiO\(_2\) may be present in the mixture. Such clusters might be disintegrated further by dispersing devices with a higher number of revolutions per minute. First experiments with such a device show promising results from optical inspection.

### 6.2.4 Derivation of the Mixture Formula

Knowing the interaction cross sections for TiO\(_2\) and CB, one obtains the mixing formula. The necessary concentrations for TiO\(_2\) and CB for a certain wavelength \( \lambda \) are obtained by

\[
\begin{align*}
c_{\text{CB}}(\lambda) &= \frac{\mu_a}{\sigma_{\text{CB}}(\lambda)}, \\
c_{\text{TiO}_2}(\lambda) &= \frac{\mu'_s}{\sigma_{\text{TiO}_2}(\lambda)},
\end{align*}
\]

where \( \mu_a \) and \( \mu'_s \) are the desired optical parameters and \( \sigma_{\text{CB}}(\lambda) \) and \( \sigma_{\text{TiO}_2}(\lambda) \) are obtained from (6.11).

### 6.3 Validation

The validity of the mixture formula for solid silicone phantoms is assessed by constructing layered phantoms with different compositions and hence different optical properties. The reflection and transmission of these phantom stacks is measured and compared to results obtained from Monte Carlo simulations from the same structure.

#### 6.3.1 Measurement Setup

The phantom structures are composed of cylindrical silicone phantoms with a radius of \( r = 55.5 \) mm. Thin layers with thicknesses between \( 6.0 < d_l < 7.5 \) mm are loosely pressed on top of a thick block with thickness \( d_b = 32.1 \) mm. The setup is illustrated in figure 6.8. The block material is only scattering with a TiO\(_2\) concentration of 2 g/l, which yields optical properties of \( \mu_a = 0 \text{ mm}^{-1}, \mu_s = 6.31 \text{ mm}^{-1}, g = 0.63 \).
Figure 6.8: Layered phantom setup to compare measured reflectance and transmittance values to Monte-Carlo simulations.

according to the mixture formula from section 6.2.4. The top layers (see Figure 6.9) can be exchanged and represent different scattering and absorbing mixtures.

A PCB (printed circuit board) was designed holding 4 photodetectors (BPW 34, Osram Opto Semiconductors, Regensburg, Germany) in a distance of 10, 20, 30 and 40 mm from the source. The square photodiodes have a side length of 2.67 mm and are wired in transimpedance mode (see appendix D.1 for details), hence the small photocurrent is converted to a voltage. From the measured voltage $V_{\text{out}}$, the incident power can be calculated as follows

$$P = \frac{V_{\text{out}}}{R_f \cdot R}$$

(6.14)

where $R_f$ is the feedback resistance of the operational amplifier (op amp) and $R$ is the responsivity of the photodetector. A simple expression for the responsivity $\mathcal{R}$ of a photodetector is given by

$$\mathcal{R} = \eta \frac{q}{h_f} \approx \eta \frac{\lambda (\mu m)}{1.23985 (\mu m \times W/A)}$$

(6.15)
Figure 6.9: Ensemble of thin layers (6 mm) of all the phantom mixtures. TiO$_2$ concentration is increasing to the right, CB concentration is increasing to the top.

where the $\nu$ is the quantum efficiency which is 0.9 for the photodetectors used. The wavelength of the laser source is 670 nm (the laser calibration curve is shown in appendix D.2). The laser is coupled to a fibre which is directly placed on top of the phantom. Figure 6.10 shows the measurement arrangement for the reflection and transmission measurements. The reflection setup shows a non-scattering (only absorbing) layer on top of the scattering block.
6.3.2 Monte Carlo Model

A computational model is constructed that resembles the measurement setup. Both the source fibre and the photodetectors, as well as the two layers itself are in contact with each other, but thin air gaps in between can not be avoided in the measurement setup. The Monte Carlo Model accounts for that with small air gaps of 0.1 mm between the source and the phantom, between the detectors and the phantom and between the two phantom layers. The computational domain is slightly larger than the phantoms and has an edge length of \( a_{cd} = 120 \text{ mm} \) and spacing between the top and the bottom to the phantom of 5 mm. The observer rectangles mimicking the photodetectors are also a square with edge length of 2.67 mm. The grid spacing in x direction is 0.1 mm, in y and z direction 1 mm. The material properties of the four top layers are summarised in the following table 6.1.

<table>
<thead>
<tr>
<th>sample id</th>
<th>( c_{TiO_2} ) [g/l]</th>
<th>( c_{CB} ) [g/l]</th>
<th>( \mu_a ) [1/mm]</th>
<th>( \mu_s ) [1/mm]</th>
<th>g</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>l1</td>
<td>2.0</td>
<td>0.0</td>
<td>0.0</td>
<td>6.31</td>
<td>0.63</td>
<td>1.44</td>
</tr>
<tr>
<td>l2</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>3.15</td>
<td>0.63</td>
<td>1.44</td>
</tr>
<tr>
<td>l3</td>
<td>0.0</td>
<td>0.1</td>
<td>0.22</td>
<td>0.0</td>
<td>0.0</td>
<td>1.44</td>
</tr>
<tr>
<td>l4</td>
<td>4.0</td>
<td>0.0</td>
<td>0.0</td>
<td>12.62</td>
<td>0.63</td>
<td>1.44</td>
</tr>
</tbody>
</table>

Table 6.1: Optical properties for the different phantom layers.

6.3.3 Results

The measurement and simulation results are compared by referencing their detected or simulated power to 1W input power. Figure 6.11 shows the results of the measurements and corresponding simulations. They show overall a good agreement.

When looking at the ratio between measured and simulated values, it can be observed that the ratio is almost constant, hence the characteristics of the light propagation can be accurately reproduced. The absolute values differ only by a certain factor which can be caused by laser drift or other error sources in the measurement. They indicate at the same time, that the mixture formula can be used to produce silicone phantoms with desired optical properties.

6.4 Summary

This chapter has explained how solid optical phantoms based on silicone rubber can be manufactured. The optical properties of these phantoms are altered by adding
Figure 6.11: Results of the simulations and measurements of the layered phantom structures.

TiO$_2$ and CB powder in different concentrations. The absorption coefficient and the scattering coefficient can thereby independently be influenced by the concentration of CB and TiO$_2$ powder, respectively. A mixing formula has been developed based
on an extensive sample series that enables the fabrication of phantoms with defined optical properties. Multi-layered phantoms have been fabricated and the reflection and transmission from these structures has been measured. The measurements show good agreement with simulation results from Monte Carlo simulations and prove the validity of the mixture formula.
7 Conclusion

7.1 Summary

This thesis provides a versatile toolbox for the investigation of light propagation in turbid media, especially in tissue, with the focus on biomedical optics. The provided tools can tackle biomedical optics from different directions supporting further development and improvements of these techniques. Prominent examples of biomedical optics are near-infrared spectroscopy (NIRS) or fluorescence molecular tomography (FMT).

The provided toolbox contains means to describe the phenomena of light propagation in tissue theoretically, and to give solutions of light propagation (in terms of three dimensional (3-D) fluence rate maps) with the help of numerical simulations. The characteristics of light propagation is dictated by the optical properties of the tissue. The thesis makes a setup available to measure these optical properties. In order to facilitate in vitro measurements, which can be employed to advance the development of biomedical optics, a recipe and guidance to manufacture solid, silicone-based tissue-mimicking phantoms was invented.

An overview of the theoretical framework that is employed to describe light propagation in tissue was given in Chapter 2. Light propagation in a turbid medium such as tissue is best described in a phenomenological way in terms of photon transport. The radiative transport equation (RTE), a first order differential equation similar to Boltzmann’s equation in statistical mechanics, governs radiation - or photon - transport in a turbid medium. The employed material model is characterised with four optical parameters, the absorption coefficient \( \mu_a \), the scattering coefficient \( \mu_s \) and the scattering phase function \( p \) with the corresponding average scattering angle \( g \). The refractive index is part of the material model as well, although refractive index changes have to be treated outside the scope of the RTE. The RTE cannot be analytically solved for arbitrary geometries and materials, but a general numerical solution approach is offered by the Monte-Carlo (MC) method.

An advanced implementation of the MC algorithm has been developed in this work and is described in Chapter 3. It is a fully 3-D implementation that was developed from scratch and combines various parts that have been only demonstrated individually before. Physically meaningful results from the MC algorithm are only
obtained if the statistical error is below a certain limit. This automatically results in a huge computational demand for structures larger than a few mm$^2$. This issue is tackled with a parallelised implementation that optimally scales on large cluster infrastructures. A novel method to calculate spatially resolved 3-D fluence rate maps was introduced. The required voxelised computation of the photon paths even allows for correct treatment of refractive index changes between materials. The novel algorithm is able to calculate the fluence rate also in weakly and non-scattering materials and is equally or even more efficient than the traditional way to attain fluence rate maps. The different novel aspects of the implementation have been validated with appropriate setups.

The results of numerical studies directly depend on the employed (optical) material parameters. The knowledge of optical parameters is therefore paramount. Optical parameters can be determined in the enhanced double-integrating spheres measurement setup presented in Chapter 4. The sensitivity of the system was improved by certain measures, such as custom-made parts. Still, the optical parameters must be determined indirectly by combining solutions from a forward model with a search heuristic that yields the parameters reproducing the measured values. A detailed MC model was constructed accounting for unavoidable losses in the measurement setup. The model delivers a lookup table for the reflectance and transmittance for a very large parameter range with more than 3'300 entries. A genetic algorithm (GA) is used to find the optimal optical parameter set from the values from the lookup table, if necessary using interpolation. The optical parameters of mouse liver tissue and human brain tissue were successfully determined with this novel approach.

Numerical studies offer the possibility to investigate certain aspects of a problem with a maximum degree of flexibility. Numerical studies are therefore an indispensable tool for development and improvement of applications in biomedical optics. Investigations of two different applications with the help of numerical studies were presented in Chapter 5: The possibilities of reconstruction of the position of a light emitting fluorophore in fluorescence molecular tomography (FMT) in a mouse, and the analysis of NIRS measurements on the human head.

Along with numerical studies, phantom materials are an important piece of the modelling toolbox. A specification for solid phantoms with tissue-mimicking optical properties was introduced in Chapter 6. Silicone rubber as matrix material is most suitable to meet the requirements for solid and durable phantoms. The scattering properties of silicone phantoms can be adjusted by adding TiO$_2$ powder, while the absorption can be adjusted independently by adding carbon black (CB) powder. A mixing formula was developed enabling customizable manufacturing of silicone phantoms with user-defined optical properties.

The recipe for optical phantoms, the accurate determination of optical properties and the versatile simulation framework provide a flexible environment for analysing
and improving biomedical optics applications.

7.2 Outlook

The different biomedical applications, for example medical diagnostic techniques such as NIRS, general imaging techniques such as diffuse optical tomography (DOT) and optical coherence tomography (OCT) or visualisation and localisation of very specific tissue types in FMT, are ultimately based on the same theoretical framework. This work has made contributions with regard to different aspects and some ideas how they can be further improved are mentioned in the following.

7.2.1 Material Properties

The refractive index is currently not treated in the frame of the RTE. It is assumed that changes in refractive index can be treated separately, mostly in the computational model. This implies that that scattering and absorption properties are not linked to the refractive index. It is however questionable if this is always the case, specially for materials with high scattering or absorption coefficients. The relation of scattering and absorption properties on the refractive index need to be further studied. A starting point for this could be the evaluation of a phantom series with very high amounts of scattering or absorbing powder.

7.2.2 Monte-Carlo Implementation

A general purpose tool that is capable to solve light propagation in arbitrary structures was developed in this thesis. Many shortcomings of this method have been successfully treated, by introducing parallelisation, import of segmented anatomical data and novel ways to obtain results. Still there is room for further improvement.

- The parallelisation works successfully, but at the moment a large cluster infrastructure is needed. The parallelisation could be adapted to take advantage of today’s massive multicore GPUs (graphic processing unit) that are available even on desktop computers. This could be done either with a dedicated CUDA implementation for NVIDIA graphics cards or with a more general adaptation for OpenCL (Open Compute Language) which can take advantage of all available processing units in a computer (CPU and GPUs).
- The definition of complex material structures is a bit cumbersome at the moment. This could be improved by either providing the ability to construct other geometric primitives (such as sphere and cylinder) and the combination thereof or provide an interface to other tools that are able to create such geometries.
• The current voxelised implementation requires the geometric structures to be approximated by staircasing. This is not a drawback for structures derived from medical images due to their anyway limited resolution. For other applications which require a smooth air-material interface for example, a tetrahedral mesh structure could be more appropriate.

7.2.3 Optical Parameters

The determination of optical parameters of tissue can be difficult due to various challenges, starting with the tissue extraction. The following ideas may be investigated.

• The effect of tissue degradation on the optical properties has to be assessed in more detail. Optical properties become only comparable, if they are determined under the exact same condition of the tissue.
• More stable measurements could probably be achieved by homogenising the tissue. Although the tissue structure would be damaged, the results could be more stable and reproducible, since the exact position where the laser beam hits the sample would have a much smaller influence.

7.2.4 Reference Materials and Phantoms

A mixture formula for solid silicone-based phantoms has been presented for the first time. A number of phantom structures has been fabricated and evaluated that form the basis for more complex phantoms.

• The dispersing of the powder in the silicone could be improved by using a special dispersing device. This could narrow the particle size distribution and prevent the sedimentation of the few large particles.
• Segmented anatomical data can be used not only as input geometry for the simulation framework but could possibly also be used as input for a 3D printer to create anatomically accurate moulds for the silicone phantoms.
• Small tubes could be embedded in the phantom to perform flow measurements, e.g. for the investigation of NIRS devices. By coupling these tubes to a life support machine, even measurements with oxygenated blood could be performed.
• The refractive index of the phantoms has not been altered until now. Maybe this is possible for silicone by adding appropriated substances directly, or other materials can be found exhibiting different refractive indices.
A Definitions in Radiative Transport

This section summarises terms and definitions used in the radiative transport formalism. The terms used to describe the quantities and the nomenclature follows largely the one of Ishimaru [32].

**Photon number** $N(r, \hat{s})$

$N(r, \hat{s})$ at a given point $r$ is defined as the number of photons per unit volume moving in the direction of unit vector $\hat{s}$ (2.15), in an element of solid angle containing $\hat{s}$ divided by that element.

**Specific Intensity** $\hat{I}(r, \hat{s})$

For a given direction defined by a unit vector $\hat{s}$, the average power-flux density $\hat{I}$ of an electromagnetic wave within a unit frequency band centered at frequency $\nu$ within a unit solid angle can be determined. This quantity $\hat{I}(r, \hat{s})$ is called the *specific intensity*[24] and is measured in $\text{W} \cdot \text{m}^{-2} \cdot \text{sr}^{-1} \cdot \text{Hz}^{-1}$ (see Figure A.1). It is also called radiance or brightness. Usually a laser source with a narrow bandwidth and a detector with a large bandwidth are used. Therefore we integrate over the frequency and will refer to the following quantity when speaking of *specific intensity*
\[ \hat{I}(r, \hat{s}) = \int N(r, \hat{s}) \cdot h \cdot c \cdot d\nu \left[ \frac{W}{m^2 \cdot sr} \right] \]  \hspace{1cm} (A.1) 

with unit of Wm\(^{-2}\)sr\(^{-1}\). If the *intensity* is the same in all directions, the radiation field is said to be isotropic at a given point.

**Fluence Rate** \(\phi(r)\)

In clinical medicine, the integral of the intensity over all directions, called the *fluence rate* \(\phi(r)\) has more practical significance than the radiance itself, because an absorbing chromophore at location \(r\) inside the tissue can absorb photons irrespective of their direction of propagation. The fluence rate is defined as

\[ \phi(r) = \int_{4\pi} \hat{I}(r, \hat{s}) d\omega \left[ \frac{W}{m^2} \right] . \]  \hspace{1cm} (A.2) 

The radiant energy fluence rate is formally defined as “at a given point in space, the radiant power incident on a small sphere, divided by the cross-sectional area of that sphere” [114].

**Average Intensity** \(U(r)\)

The average intensity \(U(r)\) is defined by

\[ U(r) = \frac{1}{4\pi} \int_{4\pi} \hat{I}(r, \hat{s}) d\omega \]  \hspace{1cm} (A.3) 

Note that the average intensity does not represent the power flow. It is proportional to the energy density.
B Sampling Stepsize and Scattering Angles

B.1 Sampling the Stepsize

To determine the stepsize of a photon, the derivation in Welch et al. [115] is followed. The stepsize of a photon describes the propagation distance of a photon without material interaction. It is calculated based on the probability for the free path of the photon \( s_1 \in [0, \infty) \). From the definition of absorption and scattering coefficients (see sec. 2.2.1), the probability for interaction in the interval \([s_1, s_1 + ds_1]\) is \( \mu_t ds_1 \), where \( \mu_t = \mu_a + \mu_s \). From the radiative transport equation (RTE) one gets

\[
\frac{d\hat{I}(s_1)}{ds_1} = -\mu_t \cdot \hat{I}(s_1).
\] (B.1)

Integration over the range \([0, s_1]\) gives

\[
\hat{I}(s_1) = \exp(-\mu_t s_1)
\] (B.2)

which represents the probability \( P\{s \geq s_1\} \) of a photon path length \( s \) to be larger than \( s_1 \). The cumulative distribution function of free path \( s \), \( P\{s < s_1\} \), is given by

\[
P\{s < s_1\} = 1 - \exp(-\mu_t s_1).
\] (B.3)

With 2.47 one obtains

\[
\xi = F(x) = P\{s < s_1\} = 1 - \exp(-\mu_t s_1).
\] (B.4)

Solving for the stepsize \( s \) yields

\[
s = -\frac{\ln(1 - \xi)}{\mu_t}
\] (B.5)

which is equivalent to

\[
s = -\frac{\ln(\xi)}{\mu_t}
\] (B.6)

if \( \xi \) is a random variable uniformly distributed in \((0, 1]\).
B.2 Sampling the Scattering Angles

When a photon is scattered, two scattering angles have to be sampled. The deflection angle $\theta$ denotes the angle between the incident photon trajectory and the new one. It is in the interval $[0, \pi]$, where the angle 0 means no deflection and $\pi$ complete backscattering. The probability distribution for the angle $\theta$ is determined by the scattering phase function (see sec. 2.2.4). The probability density function proposed by Henyey-Greenstein is given by

$$p(\mu) = \frac{1 - g^2}{2(1 + g^2 - 2g\mu)^{3/2}} \quad (B.7)$$

where $\mu = \cos(\theta) \in [-1, 1]$. The parameter $g$ is called the anisotropy factor that defines the shape of the scattering function and is conveniently equal to the expectation value of the scattering angle $\langle \mu \rangle$

$$g = \int_{-1}^{1} p(\mu) \mu d\mu = \langle \mu \rangle. \quad (B.8)$$

Applying (2.47) leads to

$$\xi = \int_{-1}^{\mu} p(\mu) d\mu \quad (B.9)$$

$$= \int_{-1}^{\mu} \frac{1 - g^2}{2(1 + g^2 - 2g\mu)^{3/2}} d\mu \quad (B.10)$$

Solving for $\mu$ gives [116]

$$\mu = \frac{1}{2g} \left[ 1 + g^2 - \left( \frac{1 - g^2}{1 - g + 2g\xi} \right)^2 \right] \text{ for } g \neq 0 \quad (B.11)$$

If $g$ approaches zero, i.e. the scattering becomes isotropic, the probability density function becomes $p(\mu) = 1/2$, with (2.47) one gets

$$\xi = \int_{-1}^{\mu} \frac{1}{2} d\mu \quad (B.12)$$

$$= \frac{1}{2}(\mu + 1) \quad (B.13)$$

and resolved for $\mu$

$$\mu = 2\xi - 1 \text{ for } g = 0 \quad (B.14)$$
If a photon is scattered at a deflection angle $\theta$, it is assumed that the azimuthal angle $\Phi$ is uniformly distributed in the interval $[0, 2\pi]$ around the incident axis. The corresponding probability density function is $1/2\pi$. With (2.47) one gets

$$\xi = \int_{-1}^{1} \frac{1}{2\pi} d\Psi$$

$$= \frac{\Psi}{2\pi}$$

and hence

$$\Psi = 2\pi \xi.$$
C Genetic Algorithm

The genetic algorithm (GA) that is employed in this work for the parameter reconstruction adopts ideas described in [117]. It is implemented using the python package DEAP [118]. Four parameters are used for the optimisation: the absorption coefficient $\mu_a$, the scattering coefficient $\mu_s$, the scattering anisotropy $g$ and the refractive index $n$. These arguments are encoded on a bit string with 10 bits per argument. This yields a minimal resolution of 0.05 for the parameter with the largest value range. In order to keep locality, Gray coding is used.

A population with 80 individuals is used and the individuals are initialised with random parameter values. The fitness of a particular individual, i.e. a certain parameter combination, is calculated as described in (4.16). After each generation, every bit of the individual’s bit string is flipped with a probability of 0.1. The individuals for the next generation are selected by performing 80 tournaments with 8 randomly selected individuals and selecting the best of the 8. Mating of two selected individuals is performed by two point crossover in one of the four parameters. The GA runs for 600 generations to yield the optimal parameters set $P_{\text{opt}} = [\mu_a^{\text{opt}}, \mu_s^{\text{opt}}, g^{\text{opt}}, n^{\text{opt}}]$.

These GA configuration has been found to produce accurate and reproducible results for a large number of samples. However, no extensive optimisation of these parameters and the operators of the GA has been performed.
D Layered Phantom Measurements

D.1 Circuit to drive Photo-diodes

The photodetectors are wired in a transimpedance mode circuit, converting and amplifying the photo-current to an output voltage $V_{out}$ which is measured. The $RC$

![Transimpedance circuit](image)

Figure D.1: Transimpedance circuit to convert and amplify the photocurrent to an output voltage.

element before $V_{out}$ is used as a low-pass filter for the output signal. The operational amplifier (op amp) used is the LTC6241 from Linear Technologies. The photo-diodes are BPW 34 from Osram Opto Semiconductors.
D.2 Laser Output Characteristic

The output characteristics of the 670nm laser is measured with a calibrated integrating sphere and is shown in figure D.2. The output power versus supply current is mostly linear, but has slight ripples for drive currents above 550 mA.

Figure D.2: Laser characteristic.
E Derivation of Absorption Coefficient of White Matter depending on oxygen saturation

The absorption coefficient can be expressed in terms of molar extinction coefficient and concentration as

\[ \mu_a = \varepsilon \cdot c \cdot \ln(10) \]  
(E.1)

It is assumed that the absorption coefficient in white matter \( \mu_a \) has contributions from water \( \mu_{aH_2O} \) and haemoglobin \( \mu_{aHb} \)

\[ \mu_a = \mu_{aH_2O} + \mu_{aHb} \]  
(E.2a)

\[ = \varepsilon_{H_2O} \cdot c_{H_2O} \cdot \ln(10) + \left[ \varepsilon_{HbO_2} \cdot c_{HbO_2} + \varepsilon_{HHb} \cdot c_{HHb} \right] \cdot \ln(10) \]  
(E.2b)

The brain density is given by

\[ \rho_{brain} = c_{H_2O} \cdot mw_{H_2O} + c_{tot} \cdot mw_{Hb} \],  
(E.3)

and the tissue oxygen saturation by

\[ SO_2 = \frac{c_{HbO_2}}{c_{HbO_2} + c_{HHb}} \].  
(E.4)

In this case, it is assumed that the total haemoglobin concentration \( c_{tot}^{Hb} \) stays constant with changing tissue oxygen saturation \( SO_2 \). With a constant brain density \( \rho_{brain} = 1.05g/ml \) and a constant haemoglobin concentration \( c_{tot}^{Hb} = 61\mu M = 61 \times 10^{-6}mol/L = 61 \times 10^{-9}mol/ml \) one obtains (from (E.3))

\[ c_{H_2O} = \frac{\rho_{brain} - c_{tot}^{Hb} \cdot mw_{Hb}}{mw_{H_2O}} = 0.058mol/ml \]  
(E.5)

where the molecular weight of water is \( mw_{H_2O} = 18.02[g/mol] \) and the molecular weight of hemoglobin is \( mw_{Hb} = 68 \exp 3[g/mol] \). The concentrations for oxy- and deoxy-hemoglobin are obtained from (E.4) as

\[ c_{HbO_2} = SO_2 \cdot c_{tot}^{Hb} \]  
(E.6a)

\[ c_{HHb} = (1 - SO_2) \cdot c_{tot}^{Hb} \]  
(E.6b)
With molar extinction coefficients for $\lambda = 780\text{nm}$ of

$$\varepsilon_{\text{H}_2\text{O}} = 0.018\text{ml/mm mol} \quad (E.7a)$$

$$\varepsilon_{\text{HbO}_2} = 70000\text{ml/mm mol} \quad (E.7b)$$

$$\varepsilon_{\text{HHb}} = 120000\text{ml/mm mol} \quad (E.7c)$$

the following absorption coefficients are obtained

$$\mu_a = 15.40 \times 10^{-3} \text{1/mm}, \quad \text{for SO}_2 = 0.55 \quad (E.8a)$$

$$\mu_a = 13.99 \times 10^{-3} \text{1/mm}, \quad \text{for SO}_2 = 0.75 \quad (E.8b)$$

which corresponds to a variation of about 10%.
Bibliography


BIBLIOGRAPHY


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List of Publications

Publications related to this thesis

Journal papers


Peer-reviewed Conference Papers


Conference Abstracts

Curriculum Vitae

Personal data
Name: Christoph Josef Böcklin
Nationality: Swiss
Date of birth: July 16, 1982
E-mail: boecklic@ethz.ch

Professional experience
11/09 – 12/14: ETH Zurich, Zurich, Switzerland
Institute for Electromagnetic Fields,
Doctorate in Electrical Engineering
Modelling Light Propagation in Tissue (PhD Thesis)

04/10 – present: SHSV, St. Gallen, Switzerland
Board member of the Swiss University Sports Federation (SHSV)
(since 2013 Vice President)

01/12 – 07/12: Acreo AB, Stockholm, Sweden
Research exchange

08/06 – 10/06: Acreo AB, Stockholm, Sweden
Fabrication of high-temperature stable
fiber bragg gratings (intern)

Education
06/08 – 12/08: ETH Zurich, Zurich, Switzerland
Simulation of InGaN/GaN nanocolumn LEDs (Master thesis)

10/03 – 12/08: ETH Zurich, Zurich, Switzerland
Master of Science ETH in Electrical Engineering

01/06 – 06/06: KTH Stockholm, Stockholm, Sweden
Study exchange

09/95 – 05/02: High School Kantonsschule Alpenquai, Luzern, Switzerland