Advanced 3D Monte Carlo Algorithms for Biophotonic and Medical Applications

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Declaration

I, Lewis McMillan, hereby certify that this thesis, which is approximately 32000 words in length, has been written by me, that it is the record of work carried out by me, or principally by myself in collaboration with others as acknowledged, and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2015 and as a candidate for the degree of PhD in September 2015; the higher study for which this is a record was carried out in the University of St Andrews between 2015 and 2019.

Date ..... Signature of candidate .....

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of PhD in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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Abstract

The Monte Carlo radiation transfer (MCRT) method can simulate the transport of light through turbid media. MCRT allows the simulation of multiple anisotropic scattering events, as well as a range of microphysics such as polarisation, and fluorescence. This thesis concerns the development of several MCRT algorithms to solve various biophotonic and medical problems. Modelling of tissue ablation, autofluorescent signals, and a theoretical quasi-wave/particle MCRT model were developed as part of this thesis.

Tissue ablation can be used to treat acne scarring and Rhinophyma, it can also be used to help enhance topical drug delivery. Currently depth of ablation is not easily elucidated from a given laser or laser power setting. Therefore, a numerical tissue ablation model is developed using MCRT, a heat diffusion model, and a numerical tissue damage model to assess ablation crater depth and thermal damage to the surrounding tissue.

Autofluorescence is the natural fluorescence of biological structures in tissue. Autofluorescence can be used as a biomarker of several diseases including: cardiovascular diseases, Alzheimers and diabetes. However, the origin of the signal is not completely clear. The effect of tissue optics on the signal, which fluorophores contribute to the signal and by how much, and how different locations on the body can effect the signal are all not well understood. This thesis presents a study of the effect of tissue optics on the autofluorescent signal. As part of this study AmoebaMCRT was created to determine the relative concentrations of fluorophores for a given autofluorescent signal.

Finally, we developed an extension to the MCRT method that allows the simulation of quasi-wave/particles. This method relies on the Huygens-Fresnel principle and the tracking of the phase of each individual photon packet. The extension, φMC, allows the modelling of complex beams that require the wave properties of light such as arbitrary order Bessel beams, and Gaussian beams. We then use φMC to predict which beam, Bessel or Gaussian, preforms "better" in a highly turbid medium.

Acknowledgements

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Abbreviations

CDF cumulative distribution function.

MCRT Monte Carlo radiation transfer.

PDF probability density function.

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Chapter 1

Introduction

The advent of the computer in the last 80 years has been a boon for society. Increasing computing power is easily available, enabling high-quality investigations, and research into topics once thought beyond human computation. One topic that high power computing has revolutionised is medicine. Computers have enabled advances in many areas including drug discovery [1, 2], patient diagnoses [3, 4], and better imaging modalities [5, 6]. One particular area of focus where computers are or will be heavily used is personalised medicine.

Personalised medicine is where instead of a patient being treated with what works on an "average" patient, the treatment is tailored specifically for the patient. This can entail having fine grained knowledge of the patient down to the genome level, to understand how various drugs or treatments will affect the patient. One particular area of research in personalised medicine is into the so called "digital twin". A digital twin as defined by A. El Saddik as [7]:

> "... is a digital replica of a living or non-living physical entity."

Digital twins are currently heavily used in engineering to predict when various machinery will need to undergo maintenance. Digital twins operate by modelling their physical counterpart. This model is updated via information from their physical counterpart which allows the digital twin to predict it's physical counterparts future behaviour. Companies like Phillips use this in their MRI machines to help schedule downtime, and predict which parts the engineer will need on site, both of which minimises the downtime of the machine which is import for the hospital/clinic [8].

At the heart of the digital twin method, is the ability to accurately model the object or living thing being studied. This can be straightforward when the twin in question is a machine, as sensors can usually be attached to the various components to get feed back on the machine's operation. Machines also have the bonus of (normally) being well understood so that modelling them is usually relatively straightforward. However, this is not as easy when dealing with living systems. First, we still do not have a complete understanding of the biology within humans. Therefore, modelling a human accurately is not possible as various assumptions and approximations have to be made. Second, to get accurate information on what is happening inside a patient, generally either ionising radiation needs to be used, or cameras inserted into the patient. Both of these cannot be done for indefinite periods without causing harm or discomfort. Therefore, continuous information on the inner functions of the body is not possible. One area where information is more readily available is the skin. Information on the skin function or dysfunction is normally diagnosed with light. Light is also used in various treatments such as photodynamic therapy and tissue ablation, over various internal and external sites on the body.

Light's interaction over the whole spectrum, from the UV to the infrared, is readily modelled with techniques such as Monte Carlo radiation transfer (MCRT). MCRT allows a digital twin model of the individual patient skin to be simulated. This can then be used to tailor treatment regimes for the individual patient, or to predict treatment outcomes for specific patients. The use of simulation techniques like MCRT allow testing *in-silico*, and can negate the need to test on humans or animals.

This thesis concerns the development of various MCRT models to help diagnose, optimise treatments and help predict which imaging modalities may be better.

1.1 Monte Carlo Method

The Monte Carlo method is a numerical analysis technique based upon random numbers, which are used to calculate unknown variables in problems [9, 10].

The earliest use of the method is in Buffon's needle experiment of the 18^{th} century [11–13]. Buffon asked the question;

"Suppose we have a floor made of parallel strips of wood, each the same width, and we drop a needle onto the floor. What is the probability that the needle will lie across a line between two strips?"

The solution to this question is: for a needle length l, strip separation s, where x is the distance from the needle to the closest line, and θ is the angle of the needle with respect to the wood strips. Then using a simple geometrical argument, a needle crosses a strip if $x \leq \frac{l}{2} sin\theta$.

x is distributed uniformly in $[0, \frac{s}{2}]$, and θ in $[0, \frac{\pi}{2}]$. Therefore the probability density function for x is $p(x) = \frac{2}{s}$, and θ is $p(\theta) = \frac{2}{\pi}$. The probability density function (PDF), is a function of a variable that gives the probability for a variable to a take a given value. The PDF is normalised over the whole range of the variable, in this case x, and θ. Thus, as x and θ are independent variables, giving a joint probability of $p(x, \theta) = \frac{4}{s\pi}$. So the probability of a needle of length l crossing a line ($l < s$) is:

$$P = \int_0^{\frac{\pi}{2}} \int_0^{\frac{l}{2} sin\theta} \frac{4}{s\pi} \, dx \, d\theta = \frac{2l}{s\pi} \tag{1.1}$$

Equation (1.1) can be used to carry out a Monte Carlo estimation of π. A simple rearrangement yields: $\pi = \frac{2l}{sP}$ where P is the ratio of needles crossing the line to the total number dropped. Laplace was the first to suggest that Buffon's needle experiment could be used to estimate π [12]. Figure 1.1 shows an example of a simulation of Buffon's needle experiment.

There are various different approaches to using the Monte Carlo method to obtain randomly sampled variables. One analytical way of achieving this is the inverted sampling method. The inverted sampling method can be summarised by the following steps for drawing a sample X_i from an arbitrary PDF $p(x)$:

1. Compute the cumulative distribution function (CDF) $P(x) = \int_0^x p(x')dx'$
2. Compute the inverse $P^{-1}(x)$
3. Obtain a uniformly distributed random number ξ in the range [0.,1.)
4. Finally, compute $X_i = P^{-1}(\xi)$

If a given problem cannot use the inverted sampling method, as it may not be possible to get a PDF or analytically invert the CDF, then the rejection method can be used. The rejection method is essentially a dart throwing method. This means that points are randomly chosen and compared to the function. If the point lies under the function then the point is accepted, if it

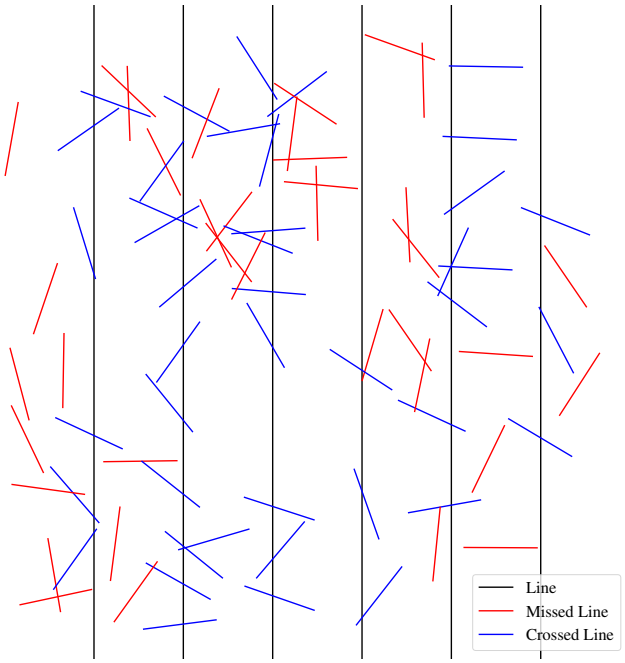

Figure 1.1: *Sample Buffon needle experiment. 100 needles are dropped on a 10 × 10 cm area with lines spaced 1.5 cm apart. If a needle lands on a line it is recorded and coloured blue, else it is red. This simulation gave a value of* $\pi \approx 3.10$.

lies above the function then it is rejected. For example, if a function, $f(x)$ that does not have an analytical PDF, we can use a PDF $p(x)$ such that $f(x) < cp(x)$ where c is a constant. Therefore sampling from $p(x)$, and if the sampled point lies under $f(x)$ it is accepted, else it is rejected. Figure 1.2 shows an example of this process.

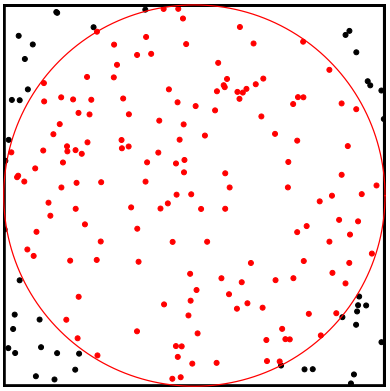

Figure 1.2: *Illustration of the rejection method for determining* π *from the area of a circle inscribed within a square. The ratio of the area of the circle to the square is* $\frac{\pi}{4}$. *Thus the ratio of darts landing in the circle to those that land outside the circle is* $\pi \approx \frac{4N_{inner}}{N_{total}}$, *where* N_{total} *is the total number of darts, and* N_{inner} *is the total number of darts that land in the circle. Using 200 darts gave a value of* $\pi \approx 3.12$

One common use of the Monte Carlo method, is to randomly sample from a spectrum. To generate a random sample from a spectrum, first the CDF of the spectrum must be calculated. This is done by first normalising the PDF, where the PDF in this case is the spectrum itself. It is normalised such that the sum of the PDF is unity. The CDF is then just the cumulative sum of the PDF. Then using the above method as described above, a random number is drawn, ξ, and the bracketing values in the CDF are found. We then interpolate to get the x value corresponding to ξ. Figure 1.3 shows the result of this process for 5×10^6 random samples.

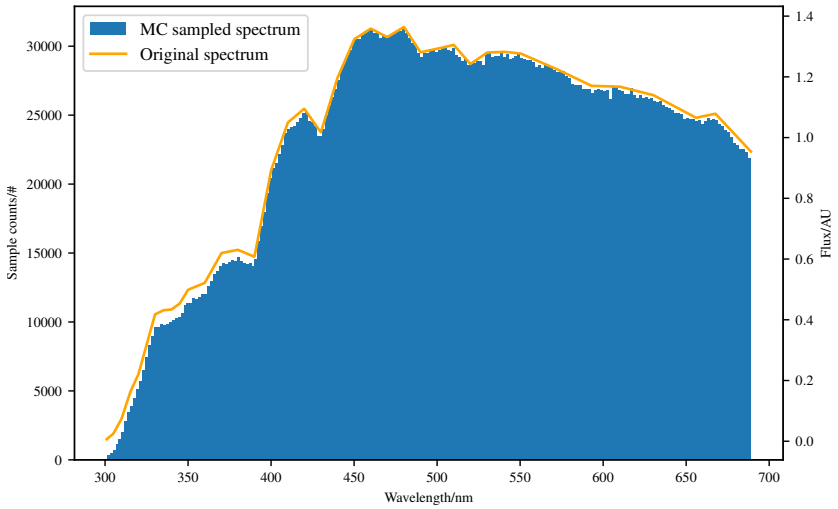

Figure 1.3: *Example of randomly sampling from a spectrum. Figure shows 100 random samples drawn to recreate a solar spectrum.*

The Monte Carlo method is used in various different disciplines. Ranging from use in the financial sector to analyse investments and stocks by simulating the sources of uncertainty which affect their values [14, 15], use in statistical analysis [16], and in modern computer generated images (see Fig. 1.4) [17, 18]. It is also widely used in astronomy [19, 20] and medicine [21, 22], to simulate the propagation of radiation through scattering (turbid) media. This technique, Monte Carlo radiation transfer (MCRT), is what makes up the bulk of this thesis and is described in depth in the following sections.

1.2 Synopsis and Thesis Objectives

Chapter 2 details the MCRT method that is used for the bulk of this thesis. Presented in this chapter are details of the algorithm and various code implementation details that underpin the whole thesis. Details of speed up techniques such as parallelisation are also presented. Finally the code is validated against other results.

Chapter 3 details the tissue ablation model. A tissue ablation model was created to predict the depth of ablation craters in tissue. The model could also be used to help optimise treatment regimes in cosmetic and medical procedures. The numerical tissue ablation model consists of 3 numerical methods: MCRT to model the light transport in the tissue, numerical heat model to model the heat diffusion within the tissue, and a numerical tissue damage model to assess the damage to the tissue due to the laser. Discussion the model, alongside validation of the model

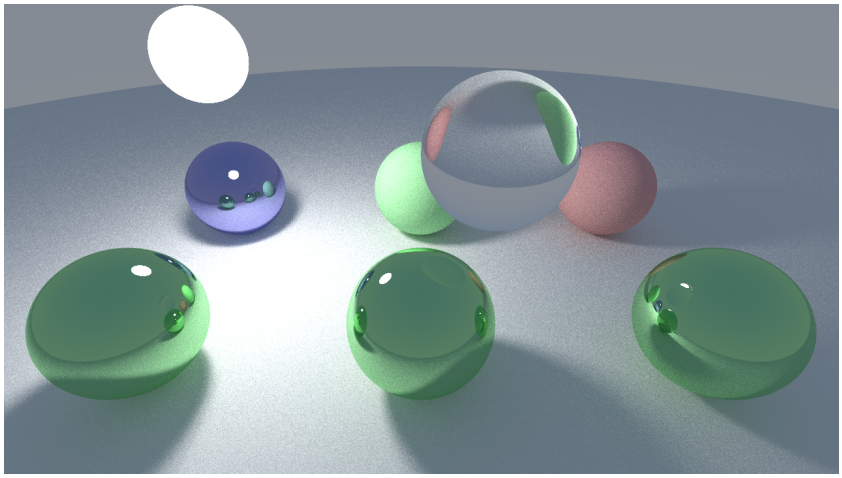

Figure 1.4: *Computer generated imagery using ray tracing. The Monte Carlo method is used to "compute radiance along ray paths between lights and the camera", to generate CGI images [23].*

against theoretical and experimental evidence is presented.

Chapter 4 presents an adaptation to the regular Monte Carlo model so that it can model wave like properties of photons including diffraction and interference. The new algorithm is validated against several common experiments that exhibit the wave like behaviour of light, including: diffraction by slits and apertures. The algorithm is also validated against real experimental data, taken by collaborators at the University of Dundee. Finally the algorithm is used to compare Bessel beams and Gaussian beam in highly turbid media, to determine which beam can image deepest.

Chapter 5 details the modelling of a novel biomarker for cardiovascular disease, autofluorescence. The theoretical groundwork for the biomarker is presented, along with discussion of how MCRT can model fluorescence. Presented alongside this is ameombaMCRT, a Monte Carlo radiation transfer simplex algorithm used to determine concentrations of fluorophores in different layers of tissue for a given spectrum.
Finally, a study of how tissue optics affect the autofluorescent signal is presented. This includes the effect of blood, melanin, and the skin thickness at different sites on the body can affect the signal.

Finally, chapter 6 concludes this thesis and presents possible future avenues of research that could be undertaken.

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